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Analysis of the new regulatory framework for active pharmaceutical ingredients in Brazil: an official pharmaceutical laboratory experience

Análise do novo marco regulatório de insumos farmacêuticos ativos no Brasil: a experiência de um laboratório farmacêutico oficial

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ABSTRACT

Introduction: The new regulatory framework for active pharmaceutical ingredients comprises three resolutions edited by the National Health Surveillance Agency, the RDC No. 359, of March 27, 2020, the RDC No. 361, of April 1, 2020, and the RDC No. 672, of March 30, 2022.These regulations start new approaches to regularize the active pharmaceutical ingredient in the country. **Objective:** To demonstrate how the internalization of the legal and health requirements established by the new regulatory framework for active ingredients was absorbed and implemented by Farmanguinhos, an Official Pharmaceutical Laboratory. **Method:** Descriptive cross-sectional study based on data collection from the legal framework edited by the Brazilian Health Regulatory Agency, and the practical experience of Farmanguinhos, the main medicines supplier to the Ministry of Health. **Results:** The main result of this study was the survey of the needs for the implementation of the new framework by the Official Pharmaceutical Laboratories, observing the greater sanitary and regulatory rigor imposed on manufacturers of active ingredients and the reflection of this in the proposed adequacy of operational procedures at Farmanguinhos. **Conclusions:** This study concludes that it is up to the Official Pharmaceutical Laboratories to intermediate and act as facilitators in the relations between active pharmaceutical ingredients manufacturers, by reviewing their procedures and editing support tools, leading to the incorporation of requirements and, in parallel, facilitating the optimization of activities and actions aimed at the implementation of a new regulatory reality, both internally and by the manufacturers of inputs.

KEYWORDS: Active Pharmaceutical Ingredient; Brazilian Health Regulatory Agency; Official Pharmaceutical Laboratory; Regulatory Framework

RESUMO

Introdução: O novo marco regulatório de insumos farmacêuticos ativos compreende três resoluções editadas pela Agência Nacional de Vigilância Sanitária em 2020, RDC nº 359, RDC nº 361 e RDC nº 672, inaugurando novas abordagens para regularização do insumo farmacêutico ativo no país. **Objetivo:** Demonstrar como a internalização dos requisitos legais e sanitários instituídos pelo novo marco regulatório de insumos ativos foi absorvida e implementada por Farmanguinhos, um laboratório farmacêutico oficial. **Método:** Estudo transversal descritivo com base no levantamento de dados do arcabouço legal editado pela Agência Nacional de Vigilância Sanitária e a experiência prática de Farmanguinhos, o principal laboratório público fornecedor de medicamentos ao Ministério da Saúde. **Resultados:** O principal resultado deste estudo foi o levantamento das necessidades para implementação do novo marco pelos laboratórios farmacêuticos oficiais, observando o maior rigor sanitário e regulatório imposto aos fabricantes de insumos ativos e a reflexão deste na proposta de adequação dos procedimentos

operacionais de Farmanguinhos. **Conclusões:** Cabe aos laboratórios farmacêuticos oficiais intermediar e atuar como facilitadores nas relações entre fabricantes de insumo farmacêutico ativo e autoridade sanitária. Assim, eles exercem um papel de impulsionador no estreitamento da relação com os fabricantes de insumos, por meio da revisão de seus procedimentos e edição de instrumentos de apoio, conduzindo a incorporação das exigências e em paralelo facilitando a otimização das atividades e ações voltadas à implementação da nova realidade regulatória, tanto internamente quanto pelos fabricantes de insumos.

PALAVRAS-CHAVE: Insumo Farmacêutico Ativo; Agência Nacional de Vigilância Sanitária; Laboratório Farmacêutico Oficial; Marco Regulatório

INTRODUCTION

Before the creation of the Brazilian National Health Surveillance Agency (Anvisa) in 1999, the health surveillance system did not include information and technical documentation on active pharmaceutical ingredients (APIs) and their manufacturers. With the improvement of the regulatory framework initiated by Anvisa back in 1999, pharmaceutical companies holding registrations in the country or intending to operate in the country were encouraged to go through an internal process of adaptation, in order to achieve the necessary training to submit a registration or registration adjustment process, in accordance with the new requirements of the legislation[1].

This path of improvement saw the introduction of the requirement for pharmaceutical equivalence and relative bioavailability studies and, in parallel, the requirement to validate analytical methods for the finished product, as well as greater control over the drug and technical information from the drug manufacturer[1].

With Anvisa's inception, the introduction and growing increase of technical requirements regarding the information on APIs from their manufacturers has become significant, as can be seen in Collegiate Board Resolutions (DRC) No. 1332, No. 1343, No. 1354, and No. 1365, of May 29, 2003, which are intrinsically linked to the importance of qualifying these suppliers.

With the improvement of Anvisa's regulatory framework, we highlight the publication of RDC No. 57, of November 17, 2009[6], which provided for the registration of APIs in Brazil, however, with a scope limited to a restricted list of APIs published by Anvisa, through separate normative instructions (IN), IN No. 15, of November 17, 2009[7], and IN No. 3, of June 28, 2013[8], limiting the obligation to register APIs to a reduced number of 20 APIs, i.e., within a universe of drugs registered in their various therapeutic classes, only 20 would have their APIs duly registered and approved by Anvisa, in the form of a dossier submitted for this purpose.

In 2014, the legislation on the registration of new, generic, and similar medicines was consolidated into a single regulation, RDC No. 60 of October 10, 2014, and consequently the technical requirements for medicines and APIs were brought into line[9].

RDC No. 60/2014 also increases the technical documentation to be assessed by Anvisa, adding the product development report, as well as the study of the API's compatibility with the excipients[9].

This resolution was updated in 2017, 2020 and 2022, with the publication of RDC No. 200, of January 29, 2017, RDC No. 361, of April 1, 2020, and RDC No. 753, of September 28, 2022, respectively, with 2020 being marked by the introduction of the new regulatory framework (MR) in Brazilian registration legislation[10,11,12].

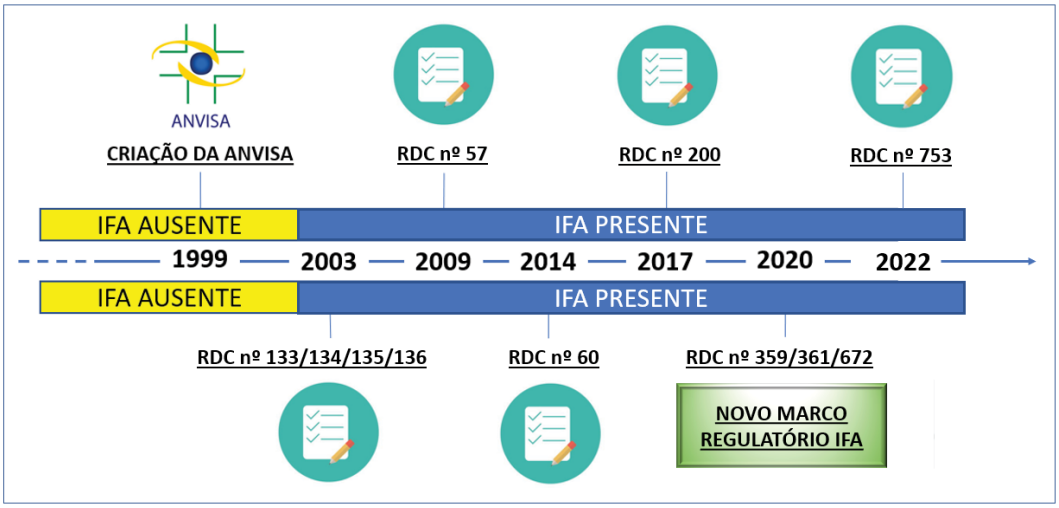
In 2022, RDC No. 200/2017 was replaced by RDC No. 753/2022, however, there were no updates to the text and determinations already contained in the new API MR, nor were there any changes to the guidelines for pharmaceutical technology requirements. The updates inaugurated by this regulation reposition the safety and efficacy requirements at a new regulatory level, since it determines two new conceptually distinct registration pathways for new and innovative drugs, while expanding the eligible paths for proving safety and efficacy[12].

The evolution of the regulatory requirements for APIs has, in its timeline, total coherence with the path taken by Anvisa focused on convergence with the best international regulatory practices, culminating in its role as a regulatory member of the *International Council for Harmonization* of *Technical Requirements for Pharmaceuticals for Human Use* (ICH), as summarized in Figure 1, with the trajectory of medicines legislation with regard to the insertion and evolution of its own legislation on APIs.

In 2020, the new API MR comprised three resolutions issued by Anvisa simultaneously, RDC No. 359, of March 27[12], RDC No. 361[11], and RDC No. 362, of March 27, revoked by the current RDC No. 672, of March 2022[14], inaugurating new approaches to API regularization in the country. One of the regulations establishes the active pharmaceutical ingredient dossier (Difa) and the letter of suitability of the active pharmaceutical ingredient (Cadifa), applicable to all APIs that are part of drug formulations in Brazil[13].

The regulation of the new MR is the result of the internalization of the guidelines of the ICH[13] management committee.

A new practice was inaugurated by RDC No. 359/2020, allowing companies without a National Registry of Legal Entities number (CNPJ) in the country and based abroad to apply for Cadifa and company registration directly with Anvisa[13].



Source: Prepared by the authors, 2023.

Figure 1. Timeline of the legislation that makes up the legal framework with the presence of the active pharmaceutical ingredient (API).

A new regulatory perspective is emerging, with the API manufacturer being responsible for answering directly to Anvisa about its processes, without the intermediation of the pharmaceutical industry.

It should be noted that the systematization of approval of Difa and Cadifa, as well as the certification of good manufacturing practices, covers all APIs to be used in medicines registered with Anvisa, i.e., all manufacturers of APIs, national or international, which have their inputs in the composition of medicines regulated by Anvisa, are subject to the provisions of the new MR[13].

The regulatory requirements are aimed at the public and private regulated sectors in equal measure. The regulations do not discriminate between APIs for neglected diseases and their manufacturers, i.e., there are no exceptions. In this way, the official pharmaceutical laboratories (LFO) are directly impacted in terms of their commitment to providing medicines to the various Public Health Programs of the Ministry of Health (MS), such as tuberculosis and malaria, and therefore by the Brazilian population's access to these treatments.

This scenario in the field of neglected diseases is due to the fact that LFOs are the main and often only suppliers of these drugs to the MS, as they are not attractive products to the private sector. Similarly, the international API industry does not have many options and companies interested in strict regulatory compliance and supply at this level of demand.

This study was carried out with the aim of demonstrating how the internalization of the legal and health requirements established by the new API MR issued by Anvisa can be absorbed by an LFO, by presenting the experience of implementing this framework by Farmanguinhos, with a focus on supporting its relationship with API manufacturers and its intermediation with the health authorities, Anvisa and the MS, contributing to maintaining the supply of medicines in the country.

The work therefore proposed changes to LFO procedures applicable to APIs and their manufacturers, covering the selection and qualification of suppliers, the registration of medicines and the product life cycle.

METHOD

In this study, the first stage consisted of a descriptive analysis with a survey of data from the health regulatory framework, comprising the RDC, IN, guides and questions and answers relating to the health registration of new, generic, and similar medicines, as well as those directly related to the subject of APIs.

The data was collected through Anvisa's official website at https://www.gov.br, using the search of the thematic library of medicines, pharmaceutical inputs, and the search through the consolidated regulatory stock, from Anvisa's own database. The survey of legislation took place in October 2022, looking at the period of publications from 1999, the year Anvisa was created, to 2022.

In order to analyze the health legislation on the registration of medicines prior to the creation of Anvisa, data from registration dossiers submitted prior to the creation of Anvisa and approved by the Ministry of Health were used, with a search of the internal database of the LFO under study.

The second stage of this study consisted of the practical experience of Farmanguinhos, an LFO linked to the Brazilian Ministry of Health. An evaluation of the procedures in force in 2022 was carried out and the procedures that presented actions and activities linked to either APIs or API manufacturers were identified.

After analyzing the selected procedures, they were compared with the new technical-regulatory requirements established by the legislation that makes up the new API MR, effective in 2022.

On the basis of this study and multidisciplinary meetings on the implementation of the new framework, adjustments were proposed to these procedures in order to incorporate the requirements of the new framework into these activities of the pharmaceutical industry. The following scenarios reported at the multidisciplinary meetings were considered in the proposed adjustments:

- The new MR affects national and international API manufacturers differently, since national and international API manufacturers are impacted differently in terms of regulation;
- The evaluation of the problems reported by manufacturers of APIs for neglected diseases for the supply of these APIs and how their qualification under Brazilian legislation has become a more rigorous process in the health field.

RESULTS AND DISCUSSION

The new MR for APIs requires their manufacturers to be more rigorous in the composition of the dossier and in direct interaction with the Brazilian regulatory body. This new legislation may have an impact on public health programs, since, according to Chaves et al.[15], the Unified Health System (SUS) is directly involved in comprehensive pharmaceutical care aimed at the supply of medicines by the public sector, which is responsible for promoting universal access, and which, in many cases, are purchased exclusively by the public sector, a specific characteristic of procurement in the Brazilian market. Consequently, this purchase may be impacted by a drop in the supply of APIs by foreign companies.

The drug production chain in the pharmaceutical industry starts with the API, so a quality or supply problem affects the entire drug production chain. As in the United States, here in Brazil the main cause of shortages is a lack of supplies, followed by other reasons. Our country is very vulnerable to this scenario, due to the exponential increase in its dependence on imports of pharmaceutical supplies[16].

On the other hand, the new MR constitutes a regulatory and health advance in the regulation of APIs and their manufacturers, as it extends its applicability to all inputs that are part of the formulation of medicines registered or submitted for registration in the country. The implementation of the MR for all APIs meets a long-standing demand from the national pharmaceutical sector, suppressing the entry of APIs from abroad, without Anvisa's approval for good manufacturing practices, at lower prices than the national industry[17].

National pharmaceutical companies are companies already regulated by Anvisa and form a manufacturing industrial park in Brazil made up of 49 active companies, mostly concentrated in the South-Southeast region of the country. Since the publication of RDC No. 69, of December 8, 2014, which provides for good manufacturing practices for inputs, adopting the international ICH Q7 guide, which deals with the same subject, Anvisa began participating in inspections of pharmaceutical companies in 2015, in parallel with the implementation of new procedures at a tripartite level, with the aim of harmonizing the local actions of health surveillance agencies[18].

According to a survey carried out by Pinto et al.[19], non-compliance with good manufacturing practices is the main reason for API recalls between 2011 and 2019. With the new framework, this scenario will change insofar as international API manufacturers will be subject to Anvisa's evaluation and only suitable manufacturers will remain on the market, mitigating recall problems. The qualification of suppliers will be supported by Anvisa and its procedures will be supported by the new API MR.

National API manufacturers, as companies regulated by Anvisa, already have an interface with the various technical areas of the agency, which has intensified with the new regulatory practices inaugurated by the new framework and has allowed them to take a regulatory advantage over international pharma companies and, at the same time, have the potential to become more competitive from a technical point of view in order to operate in more regulated markets.

On the other hand, LFOs that are committed to sustaining national health policies, especially through the development and production of drugs for neglected diseases, which are not attractive to private industry[20], are faced with the additional challenge of maintaining the adherence of these API manufacturers in the face of greater health regulation on APIs and their manufacturers, through technical support in the implementation of the new framework and a demand schedule for purchases of these APIs, resulting in a partnership between the LFO and the API manufacturer.

According to the World Health Organization, neglected diseases are those that affect vulnerable populations and have several gaps in diagnosis and treatment, delegating a devastating economic and social burden to the population[21].

In this specific case, the procedures for selecting new suppliers and qualifying them by introducing technical criteria in the light of the new framework are essential in mitigating the risk of approving international API manufacturers who will not be able to meet the requirements and will be excluded after extensive work has already been done. In the field of APIs for neglected diseases, there could be closer relations between Anvisa, the Ministry of Health, LFOs, and API manufacturers, and LFOs will have to act as intermediaries both between API manufacturers and Anvisa, facilitating the regulatory actions determined by the new MR, and between the Ministry of Health and Anvisa, being anticipators in the event of problems being identified in complying with the new framework with a possible risk of shortages.

The Brazilian association of industries of fine chemistry, biotechnology and its specialties has pointed out that a country without its own API manufacturing is vulnerable to the storms of the international scenario and cannot be leveraged without the

promotion of a consistent public policy that favors local production, giving sustainability to the health system[22].

Historically, there has been a vertiginous growth in Brazil's dependence on inputs from companies abroad. Since the 1990s, there has been a deterioration in the competitiveness of the national industry, leveraged by the process of opening up trade[23]. As a result, most of the new API framework's applicability falls to international drug manufacturers, among which China stands out as the main supplier of APIs and intermediates[24].

Thus, we remain dependent on international manufacturers, and this scenario is worsened by the possibility that manufacturers of these APIs abroad will not adhere to the strict criteria of the new MR, represented by the high standard of ICH regulatory requirements, incorporated in documents, studies and technical evidence required by the new MR, and their loyalty to the Brazilian MR is extremely important, since they are the main suppliers of regularized products in the country.

Isn't it time to give a boost to national pharma companies? One way would be to offer incentives to these companies, with the aim of boosting their API portfolio, with prerogatives for companies working with APIs for neglected diseases, reducing dependence on these inputs from abroad and the risk of these companies giving up operating in Brazil due to Anvisa's regulatory requirements.

Activities of an official pharmaceutical laboratory impacted by the new regulatory framework

After surveying the regulatory framework until 2022, Farmanguinhos' standard operating procedures that have activities related to or affected by the requirements of the new MR were surveyed.

The procedures directly affected by new activities inherent to the introduction of the new MR were related to: the selection process for candidate suppliers; the qualification of API suppliers; the quality and regulatory requirements that must be met during the duration of the drug's registration, established in the documents designated in the pharmaceutical industry as the quality agreement and change control; registration and post-registration; and the drug's purchasing and production process.

The new MR has changed the dynamics of interaction between the API manufacturer, the drug manufacturer, and the regulatory body in Brazil, as well as establishing a new administrative channel directly with the API manufacturer when it comes to analyzing its documentation, relieving the pharmaceutical industry of this responsibility in the drug dossier. On the other hand, the new framework delegates to the pharmaceutical industry a greater need for systematic monitoring and control over the drug manufacturer, assuming a key role in controlling the API's life cycle, which will be reflected in the control employed in its acquisition, release, and use in the production and shipment of drugs manufactured by LFOs.

With the new MR in force, the flow of preparing the dossier for registration and/or alteration of registration has changed, making the program of face-to-face audits by LFO teams strategic, allowing the partnership to be strengthened in order to optimize the scope of alignments and understanding of the quality criteria required by Anvisa, constituting an essential relationship for mitigating the risks of non-compliance with the regulatory impacts arising from the API's life cycle.

The proper implementation of the new MR by the LFOs, as well as their work with drug manufacturers to ensure its internalization and compliance, will have a major impact on the role of the 21 LFOs, distributed throughout the country and linked to the state and federal governments, since they supply SUS with 30% of the medicines[25], filling supply gaps in the field of infectious and neglected diseases and reducing the country's dependence[26].

Considering that in many cases the API represents 70% to 80% of the final price of the medicine and that in Brazil[23], even though LFOs are dependent on inputs from domestic or foreign industries[27] and have not historically been producers of raw materials, it is clear that their role is essential both in terms of the formulation and the cost of this medicine, and it is possible to admit that procurement problems with the API due to technical or cost problems will have a direct impact on the supply and access to these medicines.

The compilation of the Difa document format into the *Commom Technical Document* (CTD) standardized the structure of Difa from different sources. However, the documentary similarity of the manufacturers is not enough, since three additional parameters are important, such as the availability of the API, its cost and quality[28].

LFOs are easily confronted with problems in finding manufacturers of APIs for neglected diseases who are able to reconcile these parameters and, for this reason, by providing all the support and monitoring of the process of implementation of this framework by the drug manufacturers, especially the international ones, they can help them to establish a new way of working with the Brazilian health authority, Anvisa, based on the main international regulations in the area of pharmaceutical supplies.

Private and public laboratories are distinctly affected, in that high-cost, high-quality APIs are more easily adapted to the new framework, while low-cost, volume-purchased APIs for neglected diseases are likely to fail to meet the quality requirements, given their manufacturers' resistance to adapting to the new framework. One example is the refusal of these manufacturers to carry out stability studies in climate zone IVb, which is required for supply to Brazil[29].

In some cases, the LFO can provide active support, such as in the case of the stability study, and offer to carry out the study in order to guarantee the maintenance of supply to Brazil and mitigate the risk of shortages.

LFOs, as public laboratories, must comply with specific procedures for the acquisition of supplies in general through tendering processes.

There is no segmentation of health legislation for LFO, however, several activities of an LFO are governed by a specific legal framework, such as the API acquisition system and its purchase, governed by the Auction Law, Law No. 14,133, of April 1st, 2021, which establishes general bidding and contracting rules for direct public administration. This process becomes even more distinct when reconciling the need to buy at the lowest price and compliance with technical requirements, in order to comply with ANVISA and the drug's health registration.

It is therefore proposed that the Term of Commitment be included in the procedure for selecting candidate companies to supply API to the LFO, making it a prerequisite for proceeding with the subsequent stages.

The Term of Commitment will inform applicants of the new terms on the API manufacturer's relationship with the Brazilian health authority and with the LFO itself and will refer to new technical requirements in the light of the provisions of the new MR, delimiting the participation for the next stages of only applicants willing and aware of their commitments based on the requirements brought by RDC No. 359/2020, which establishes Difa and Cadifa.

The preliminary check can include a questionnaire to the API manufacturer containing objective questions aimed at understanding the degree to which these laboratories are aware of and adhere to the new MR.

Chart 1 presents a model questionnaire with questions addressed to the technical/quality area of the API manufacturer, with the aim of mapping the stage of compliance or feasibility of compliance that these companies have. This questionnaire is not intended to be an exclusionary document, but rather a subsidy for an in-depth risk analysis in the qualification of this supplier.

In addition to the information provided by the questionnaire to support the risk assessment, it can show the stage of compliance with the new MR that a particular drug manufacturer is at, as well as whether or not it is feasible to adapt to the criteria imposed by this framework.

Supplier qualification procedure

The operational procedure for qualifying API suppliers must consider the new requirements delegated to drug manufacturers with the new API MR and this analysis, together with Anvisa's certification process, increases the regulatory rigor in qualifying these suppliers.

These procedures applied in the various stages that make up the entire API supplier qualification process are essential to ensure the selection, qualification and certification of drug manufacturing companies that adhere to the determinations imposed by Brazilian health legislation, as well as guaranteeing the maintenance of this supplier's compliance with health requirements, without jeopardizing the supply of these APIs, which are indispensable to the manufacture of medicines.

Figure 2 summarizes the main steps to be taken in supplier qualification within the context of a pharmaceutical laboratory's operations.

Risk analysis in supplier qualification

Risk management is one of the most recent practices internalized in international regulatory requirements relating to the quality of medicines. Risk analysis is an important tool for detecting the level of the future supplier's ability to adhere to the new framework and, if appropriate, its exclusion at this stage.

RDC No. 672/2022 establishes conditions for compliance with good API manufacturing practices, which are covered by the Brazilian health authority, considering the results of international authorities and audits by drug manufacturing companies, as well

Chart 1. Exploratory questionnaire model: checking the *status of* manufacturers of active pharmaceutical ingredients in the light of the new regulatory framework.

Questionnaire
• Does the company supply this API to other pharmaceutical companies in Brazil?
• Is the manufacturer aware of the Brazilian legislation that makes up the new regulatory framework?
• Does the Difa manufacturer/holder have a Cadifa for this API and/or another API?
• If it doesn't have a Cadifa, is the company registered with Anvisa (if international) or regularized (if national)?
• Does the company have a CBPF issued by Anvisa for this API?
• Does the company have a CPBF issued by an authority belonging to the PIC?
• Does Difa comply with RDC No. 359/2020?
• Is Difa in *Common Technical Document* (CTD) format?
• Does the international company have a *Certificate of Suitability* (CEP) for this API?
• Does the international company have technical representation in Brazil (subsidiary or representative company)?

Source: Prepared by the authors, 2023.
API: Active pharmaceutical ingredient; Difa: Active pharmaceutical ingredient dossier; Cadifa: Active pharmaceutical ingredient dossier suitability letter; CPBF: Good manufacturing practice certificate; PIC: *Pharmaceutical Inspection Cooperation Scheme;* RDC: Collegiate Board Resolution.

as non-conformities reported in inspection reports and their corrective actions taken.

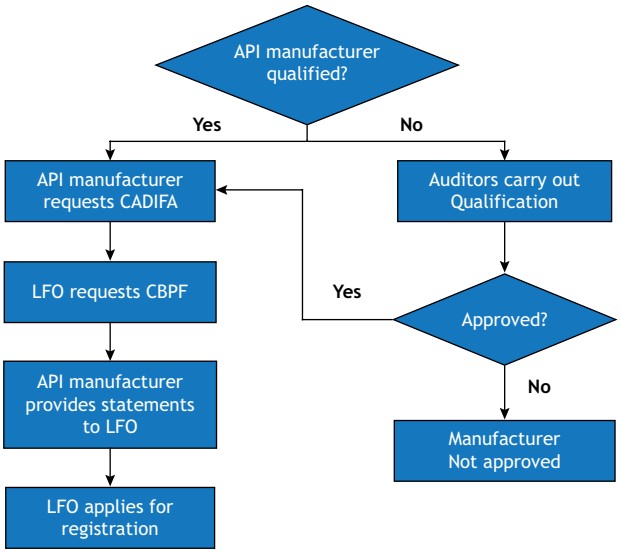
In addition, it is encouraged that a risk analysis be carried out and a scoring scale be determined for the criterion "Regularization of the Drug Manufacturer at Anvisa", assigning the following scales: high, medium, and low risk.

Chart 2 compiles the criteria proposed for the risk analysis and their respective risk classification of the API manufacturers subject to the supplier qualification process.

Quality audits in supplier certification

On-site quality audits are essential in verifying the efficiency and effectiveness of the quality system implemented and compliance with good manufacturing practices, which is supported by the Anvisa regulation that established the general guidelines for good manufacturing practices, RDC No. 658/2022[30].

Within the scope of the inspection program for international API manufacturing establishments instituted by Anvisa, and also through the establishment of Cadifa, the program of face-to-face audits by a team of LFO auditors becomes strategic, allowing for a closer partnership in order to optimize the scope of alignments and understanding of the quality criteria required by Anvisa, constituting an essential relationship for mitigating the risks of non-compliance with the regulatory impacts arising from the API life cycle.



Source: Prepared by the authors, 2023.
API: Active pharmaceutical ingredient; Cadifa: Letter of suitability of the active pharmaceutical ingredient; CBPF: Good manufacturing practice certificate; LFO: Official pharmaceutical laboratory.

Figure 2. Main stages in the qualification of suppliers of active ingredients after the regulatory framework.

Provision for the new regulatory framework in quality agreements

The qualified API supplier must comply with the requirements established for maintaining its certification status as an API supplier, such as compliance with the provisions of the quality agreement, especially regarding commitments to communicate changes, their notifications and submissions to Anvisa.

In order to assist these change processes and their proper unfolding, control and monitoring activities can be used, as seen in Figure 3.

Flow of suitability of the API and drug manufacturer prior to the application for registration, during registration, and post-registration

After the supplier qualification process, both API manufacturers and drug manufacturers will be able to proceed with the following steps towards obtaining the Cadifa and sanitary registration of the drug.

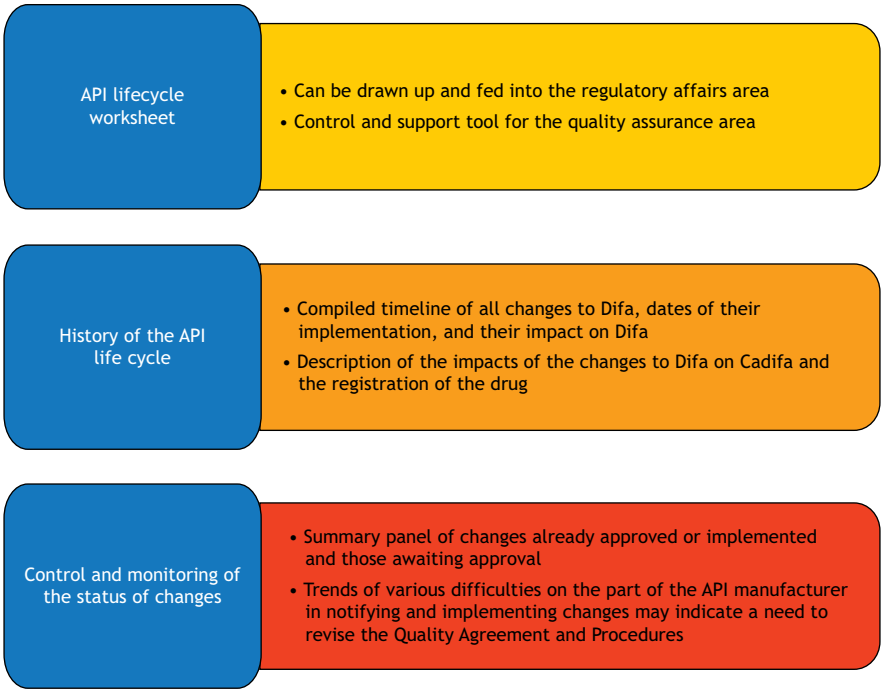
The flow shows the steps prior to the application for registration or post-registration required with the new MR:

- LFO sends legislation/guidance to the API manufacturer and, if applicable, provides appropriate training;
- LFO provides technical support and intermediates the company registration process and the submission of the Cadifa by the API manufacturer;

Chart 2. Risk criteria in light of the new regulatory framework for active pharmaceutical ingredients according to RDC No. 359/2020 and RDC No. 361/2020.

	Anvisa regularization	Performance in the Brazilian market	Difa adequacy
High risk	Drug manufacturers without Cadifa and CBPF or satisfactory audit results	Companies that have not started supplying API to Brazil	Companies with Diff not complying with the quality module (3.2.S)*
Medium risk	Drug manufacturers without Cadifa and with a regulatory structure in Brazil (subsidiary or representative) and with CBPF or satisfactory audit results	Companies that do not supply the API in question, but supply other APIs to Brazil	Companies that have the information requested in module 3 but do not have the module in CTD format (ICH m4Q (R1))
Low risk	Drug manufacturers with Cadifa and CPBF issued by Anvisa or PIC authority	Companies already supplying the API in question to Brazil	Companies that have module 3 (3.2.S) of DRC No. 359/2020, ICH M4Q (R1) and CTD format

Source: Prepared by the authors, 2023.
*Module: set of documents that make up parts of the dossier in CTD format, as provided for in RDC No. 359/2020.
Anvisa: Brazilian National Health Surveillance Agency; API: Active pharmaceutical ingredient; Difa: Active pharmaceutical ingredient dossier; Cadifa: Letter of suitability of the active pharmaceutical ingredient; CPBF: Good manufacturing practice certificate; PIC: *Pharmaceutical Inspection Cooperation Scheme*; RDC: Collegiate Board Resolution; CTD: *Common Technical Document*; ICH: *International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use*.



Source: Prepared by the authors, 2023.
API: Active pharmaceutical ingredient; Difa: Active pharmaceutical ingredient dossier; Cadifa: Letter of suitability of the active pharmaceutical ingredient.

Figure 3. Activities for controlling and monitoring change processes.

- API manufacturer requests Cadifa through Anvisa's electronic application system, known as the Solicita system;
- LFO submits the Good Manufacturing Practices Certification application to the API manufacturer;
- LFO files the application for registration/post-registration of a drug related to Difa and its respective manufacturer.

The registration processes for medicines belonging to the categories of new, innovative, generic, and similar must be instructed in accordance with the documentary *checklist* established by RDC No. 753/2022.

The assessment and decision on the specific post-registration application to be submitted must come from the communication of API manufacturers with Cadifa whenever there are changes to Difa. The drug's registration holder must assess whether there has been a revision to Cadifa and file the corresponding post-registration changes, in accordance with the provisions of RDC No. 73/2016, as amended by RDC No. 361/2020.

How can the life cycle requirements of the active pharmaceutical ingredient dossier be incorporated and documented?

Change control documentation is a crucial tool in the correct chain of approvals and implementation of changes by both parties, the API manufacturer, and the drug manufacturer.

Through monitoring, it is hoped to obtain data on the updated versions of the documents, so that they can be disseminated internally to the sectors concerned and new data can be supplied to the computerized system itself, if appropriate, regarding the versions approved for use as of a set date.

Knowledge of and access to the versions is intended to mitigate the risk of purchasing and using APIs that do not comply with the conditions approved in the Cadifa and in the corresponding drug's health registration.

Preferably, the computerized business management system adopted by the company will be able to assign a changeable version control number to the approved API, coupled with its coding or, if independent, linked to it.

Monitoring the implementation of the change (active pharmaceutical ingredient manufacturer vs. drug manufacturer)

The LFO must draw up a system for monitoring changes made to the DIFA and the registration of the drug, taking on the key role in controlling the life cycle of the API, which will reflect the control employed in the acquisition of APIs, their release and use in the production and dispatch of the drugs manufactured by the LFO, with a guarantee that the API used in the formulation complies with the DIFA approved by Anvisa for this drug.

Such monitoring by LFOs will also allow them to provide technical support to API manufacturers, mitigating the risk of health violations, such as the API manufacturer mistakenly exporting batches of APIs that do not comply with the version approved for the DIFA and the drug in question.

Control of the purchase of active pharmaceutical ingredients in accordance with the new regulatory framework for production

Pharmaceutical companies have their own administrative management systems. Since LFOs are public companies, they use the electronic information system (SEI) in their procurement processes for APIs and other inputs used in the manufacture of medicines. In particular, for APIs purchased in the routine production of medicines, preliminary information from the manufacturer of the drug approved for this medicine must be included in the purchase justification. With the implementation of the new API MR, it is essential that additional data is added to reference the correct characteristics of the approved API and the corresponding Cadifa, as well as the code/reference of the Difa in question. In parallel, the API lifecycle spreadsheet containing the approved changes to the API within the drug registration process serves as a support tool.

CONCLUSIONS

The evolution of the regulatory requirements for the API is completely consistent with the path Anvisa has followed, focused on convergence with the best international regulatory practices, culminating in its role as a regulatory member of the ICH.

It is essential that, in parallel with the improvement of the regulatory framework applicable to APIs and the drugs that use them, public policies aimed at public health programs for neglected diseases take into account this new regulatory scenario, which on the one hand is challenging for national and international API manufacturers and drug manufacturers, but on the other hand raises the level of safety and efficacy of these inputs and drugs, as well as making national API manufacturing companies more competitive on the international market.

The increased sanitary rigor applicable to all manufacturers of pharmaceutical ingredients and, consequently, to all drug formulations brought in by the new MR of active ingredients, should motivate closer relations between LFOs, API manufacturers, Anvisa and the MS, with a view to maintaining the supply of quality-assured drugs and the continuity of an adequate supply to meet the needs of the population.

The results of this study show that it is up to the LFO to mediate and act as a facilitator in the relationships and activities between the LFO, API manufacturers and the health authority regulating the new MR, playing a driving role in strengthening the relationship with API manufacturers by reviewing its operating procedures and publishing support instruments, such as manuals, which can mitigate the main obstacles to their absorption of the new MR, leading to the incorporation of the requirements and at the same time facilitating the optimization of activities and actions aimed at implementing the new regulatory reality, both internally by the LFO and by the API manufacturers.

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Authors' Contribution

Costa SM - Conception, planning (study design), analysis, data interpretation, and writing of the work. Boas MHSV, Rito PN - Conception, planning (study design), data analysis and interpretation. All the authors approved the final version of the work.

Conflict of Interest

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