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Review Article

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Drug Product and Drug Substance (CADIFA) Registration process in Brazil

Pankaj P. Nerkar [a,*], Atul P. Patil [a], Mayuri V. Ahire [a], Suhas R. Mahajan [b], Swati D. Raysing [a]

[a] *R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur.*
[b] *Department of Pharmaceutics, H.R. Patel Institute of Pharmaceutical Education and Research, Shirpur.*

Abstract

There is a significant demand for improved healthcare and advanced pharmaceuticals in Brazil, presenting lucrative opportunities for foreign investors. However, engaging in business activities in Brazil can be challenging due to various factors. The process of registering pharmaceutical products in the country is time-consuming. Moreover, the highly regulated, complex, and fragmented Brazilian healthcare system, which is prone to corruption, can pose significant difficulties for small and medium-sized enterprises lacking the necessary financial resources and market knowledge. To comply with regulations, companies must provide detailed information about their drug products, including specifications, leaflets/labels, precautions, and other crucial details, all of which must be submitted in Portuguese in a comprehensive dossier. It typically takes close to a year to complete the medical registration process. In Latin America, specifically Brazil, Argentina, and Chile, there is a push to promote the registration of generic products by reducing the associated costs. Despite the obstacles and issues faced, Brazil's population of nearly 200 million people, its strategic position within Latin America, and its growing economy collectively present an appealing and promising market for various pharmaceutical sectors, offering potential for profitability.

Keywords: CADIFA, DRA, Brazil, Drug Registration, ANVISA, Generic Drug, CMC

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*Corresponding author

1. Introduction

Brazil is currently attracting significant investments and generating high expectations among international pharmaceutical companies. With a population exceeding 200 million people and ranking as the world's eighth largest market for prescription medicines, Brazil offers immense opportunities. ANVISA, the Brazilian regulatory agency, holds considerable influence and is recognized as a leading authority in Latin America and globally. This makes registering drug products in Brazil an attractive strategy for pharmaceutical companies from developed nations, including those facing market saturation or financial challenges. However, it is important to note that the registration process for non-Brazilians is becoming increasingly intricate, time-consuming, and complex. Unlike the conventional approach followed by most national regulatory agencies, which provide guidance through documents such as guidelines and instructions, the regulatory framework in Brazil relies on a legal and hierarchical structure. This includes decrees, resolutions, ordinances, laws, and established acts, rather than a comprehensive guidance document. (1) Table 1 provides a fundamental summary of Brazil, offering a concise understanding of the country. (2) On the other hand, Table 2 elucidates the definitions associated with different categories of drugs. The drug registration process in Brazil is illustrated in Figure 1, outlining the sequential steps involved.

Table 1. Fundamental Summary of Brazil

Regulatory Agency	**ANVISA (Foundation year: 1999)**
CMC Complexity	High
Regulatory agency activity	High

Critical or Country Specific CMC Requirements:
Stability Requirements: In Brazil necessitate conducting specific tests per dose form within Zone IVB, within duration of 6 months accelerated stability followed by 6 months of long-term stability. Extrapolation beyond 24 months of shelf life is not permitted.
Analytical validation: A thorough validation report must be provided, encompassing individual concentrations, analytical responses, final results, calculations, statistical data, acceptance criteria, and discussion on results. Compendia methods need partial validation to demonstrate their adequacy in terms of accuracy, precision, and selectivity. Linearity should be established using at least 5 concentrations in triplicate, while precision needs to be extensively evaluated.

Post-Registration Guidance: is highly comprehensive and demands meticulous attention to detail, although it does not align with Common Technical Document content.

For Large Molecules: Shipping validation is required.

Average approval timelines:

FDC: Granted a shelf life of 24 months, while emerging components have a shelf life of 15-18 months.

Age Range: Specified for this context is between 6 and 14 months.

In cases where ANVISA fails to initiate the review process within the legally stipulated time frames following submission, conditional approval can be granted.

Other relevant information

ANVISA recently became a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in 2016. While ANVISA plans to align its guidance with ICH, it will also retain certain country-specific standards. ANVISA was appointed to the ICH Management Committee in November 2019 and will hold this position until 2021.

The implementation of the Common Technical Document (CTD) format is still pending, but the M4 guidance is already in effect in the respective domain.

Local release testing is mandatory for small molecules.

ANVISA has established an expedited pathway for rare diseases and priority submissions. Additionally, ANVISA is currently in the application process of becoming a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and holds the status of "Applicant."

Table 2. Definitions of Drug Category

Drug Category	Definitions
New Drugs	Innovative products undergo rigorous non-clinical and clinical studies to demonstrate their safety, efficacy, and quality prior to being registered with ANVISA. (3)
Branded Generics	Products that share identical active ingredient(s), concentration, dosage form, administration route, dosage administration, and therapeutic recommendations as the reference drug registered with ANVISA. The only permissible differences are related to the product's size, form, expiration date, packaging, labelling, excipients, and it must always be distinctly identified by its trade name or brand name. (4)
Non-Branded Generics (Similar Drugs)	Products that possess identical active ingredient, formulation, pharmaceutical form, mode of administration, dosage, and indication as the reference drug already approved by ANVISA. These products are designed to be interchangeable with the reference product, ensuring their compatibility and equivalence. (5)

2. Drugs Registration Process in Brazil

Figure 1. Steps of Drugs Registration in Brazil

2.1 Structure of Registration Dossier

The registration dossier in Brazil follows a two-part structure and is prepared in the electronic Common Technical Document (eCTD) format. Part 1, corresponding to Module 1, comprises administrative data and local knowledge. Part 2, encompassing Modules 2, 3, 4, and 5, contains summaries of pre-clinical investigations, chemistry, manufacturing, and controls (CMC) information, nonclinical data and reports, and clinical data and reports. A visual representation of the required CTD modules in the registration dossier is provided in Figure 2. Furthermore, Table 3 illustrates the details of Module 2, while Tables 4, 5, 6, 7, and 8 present the contents of Modules 1, 2, 3, 4, and 5, respectively. The ANVISA review process for the registration dossier is outlined in Figure 3. (6)

2.2 CTD Module

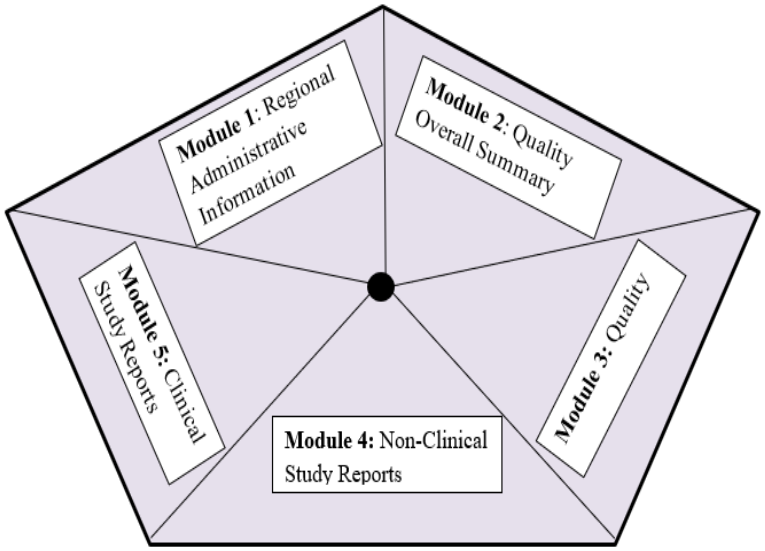

Figure 2. CTD Module

Table 3. Module 2 Quality Overall Summary

Module 2: Quality Overall Summary	
Non-clinical overview	Clinical overview
Non-clinical summary	Clinical Summary

2.3 Content of Registration Dossier

Table 4. Dossier content of Module 1

Dossier Content	**New Drug**	**Branded Generic Drug**	**Similar Drug**
Module 1			
Sanitary license of local representative	√	√	√
Local representative operating authorization	√	√	√
Registration of local Pharmacist at professional council	√	√	√
Petition form	√	√	√
Justification for product registration	√	√	√
Labelling of different presentations	√	√	√
Previous Communications with ANVISA	√	√	√
CPP issued from the HA in country of origin	√	√	√
GMP certificates issued from the HA in country of origin	√	√	√
GMP certificates granted by ANVISA	√	√	√
Registration status worldwide	√	√	√
Pharmacovigilance data	√	√	√
Product labelling in Portuguese	√	√	√
TSE information	√	√	√

Table 5. Dossier content of Module 2

Dossier Content	**New Drug**	**Branded Generic Drug**	**Similar Drug**
Module 2			
2.1 Table of contents of Module 2	√		
2.2 Introduction	√		
2.3 Quality Overall Summary	√		
2.4 Non-clinical Overview	√		
2.5 Clinical Overview	√		
2.6 non-Clinical	√		
2.7 Clinical Summary	√		

Table 6. Dossier Content of Module 3

Dossier Content	New Drug	Branded Generic Drug	Similar Drug
Module 3			
3.1 Table of contents of Module 3	√	√	√
3.2 Body of data	√	√	√
3.2.1 Drug Substance	√	√	√
3.2.2 Drug Product	√	√	√
3.3 Literature references used in Module 3	√	√	√

Table 7. Dossier Content of Module 4

Dossier Content	New Drug	Branded Generic Drug	Similar Drug
Module 4			
4.1 Table of contents of Module 4	√		
4.2 Study reports	√		
4.2.1 Pharmacology	√		
4.2.2 Pharmacokinetics	√		
4.2.3 Toxicology	√		
4.3 literature references used in Module4	√		

Table 8. Dossier Content of Module 5

Dossier Content	New Drug	Branded Generic Drug	Similar Drug
Module 5			
5.1 Table of contents of Module 5	√		
5.2 Tabular listing of all clinical studies	√		
5.3 Clinical study reports	√		
5.3.1 Reports of biopharmaceutic studies	√		
5.3.2 Reports of human pharmacokinetic (PK) studies	√		
5.3.3 Reports of human pharmacodynamic (PD) studies	√		
5.3.4 Reports of efficacy and safety studies	√		
5.3.5 Reports of post-marketing experience	√		
5.3.6 Case report forms and individual patient listings	√		
5.4 Literature references used in Module 5	√		
BE Studies		√	√

2.4 ANVISA GMP Inspection

The content included in the application for GMP inspection:

- A completed, stamped, and signed petition form.
- A valid GMP certificate issued by the health authorities of the originating country. Certificates in English or Spanish are accepted without requiring a sworn translation.
- Two types of master files: Plant Master File (AMP) and Site Master File (SMF).
- An Inspection Report from other health authorities in the country of origin, if available, along with the Periodical Product Review (RPP).
- The inspection schedule set by ANVISA involves the following steps:
- Approximately 6 months after receiving the inspection request, ANVISA conducts an inspection of the production facility.
- Following the inspection, ANVISA grants the company the Good Manufacturing Practices certificate within a period of 45 to 60 days.

2.4.1 Requirements for Local Testing

- The responsibility for conducting comprehensive quality control testing on finished products, adhering to standards and registered test procedures approved by ANVISA, lies with the importer in Brazil.
- The frequency of testing is determined by the volume of exports to Brazil annually, as follows:

  i. If the importation of each medicine exceeds 8 shipments per year, testing is conducted.

  ii. For each medicine, 8 shipments are imported annually, divided into 2 batches, specifically for testing purposes. (7)
- The duration of each local test is determined by the product specifications that require testing. The timeline for ANVISA's review process is provided in Table 9.

2.5 ANVISA Review Process of Registration Dossier

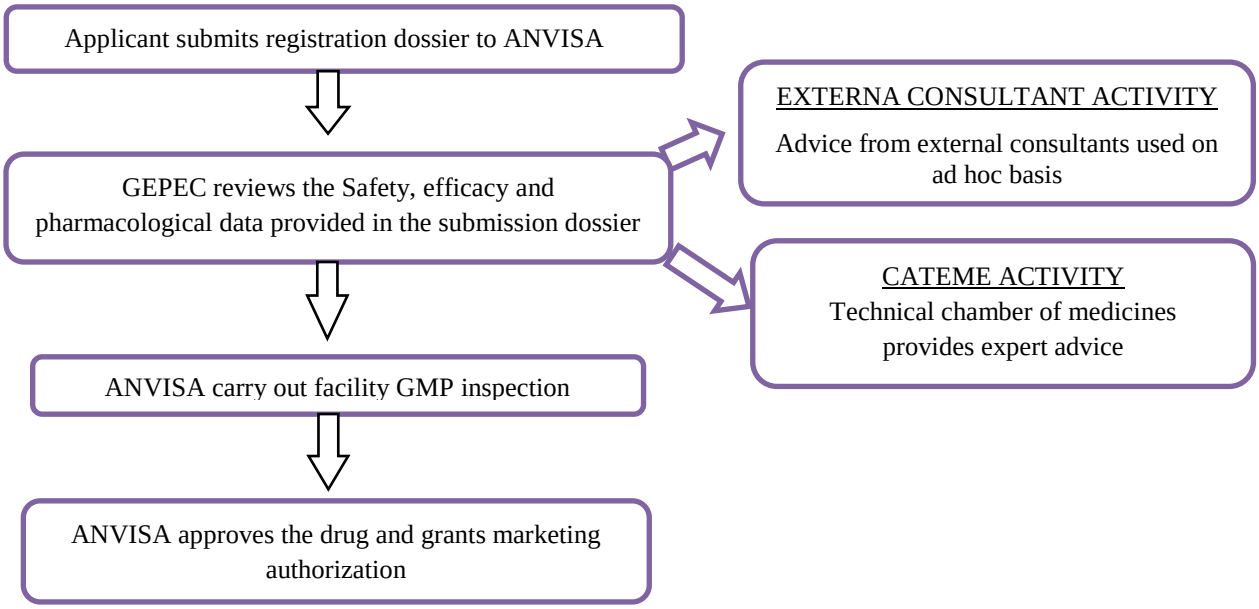

Figure 3. ANVISA Review Process of Registration Dossier

2.6 ANVISA Review Timelines

Table 9. ANVISA Review Timelines

PRIORITY REVIEW		STANDARD REVIEW	
Registration	Post-approval Changes	Registration	Post-approval Changes
120 days	60 days	365 days	180 days

3. CARTA DE ADEQUABILIDADE DO DOSSIÊ DE INSUMO FARMACÊUTICO ATIVO (CADIFA):

A DIFA (Dossiê do Insumo Farmacêutico Ativo) is certified by CADIFA (letter of appropriateness of the active pharmaceutical ingredient) to comply with the requirements stated in Resolution - RDC no 359/2020. CADIFA, being an administrative document, verifies that the tests outlined in the standard effectively manage the quality of the active pharmaceutical ingredient. It is important to note that a CADIFA does not substitute a certificate of analysis and does not provide a guarantee regarding the quality of a specific batch of API. The assessment of CADIFA application does not aim to confirm Good Manufacturing Practice compliance, although it is the responsibility of the manufacturer to ensure that the API is produced in accordance with GMP regulations. A CADIFA certificate cannot be used as a substitute or equivalent to a GMP certificate. Both a current CADIFA and GMP certificate are essential for the acceptance of a related marketing authorization or post-approval change application. To obtain a CADIFA, a DIFA must be submitted to ANVISA. The CADIFA application should be submitted prior to or concurrently with the marketing authorization or post-approval change application. If a CADIFA has already been issued for the API, the DIFA holder must provide either a copy of the CADIFA along with the declaration access filled out on behalf of the Marketing Authorization Holder by the DIFA holder or a letter to the MAH containing the DIFA's Reference Number, granting permission to use the DIFA as part of a marketing authorization or post-approval change application. In the drug product marketing authorization or post-approval change application, the MAH must provide ANVISA with the DIFA Reference Number, indicating it through the "CADIFA Process Notification" numbers 11721 (registration) and 11722 (post approval change).

To ensure a smooth process, it is important to include both the DIFA reference number and the ANVISA GMP certification application in the marketing authorization/post-approval application. The DIFA reference number should be included in the ANVISA GMP certification application form. ANVISA recommends following the following order of applications:

- Application for CADIFA
- Application for ANVISA API GMP certificate
- Application for marketing authorization/post-approval variation. Table 10 provides the deadlines for post-approval changes and marketing authorization applications.

Table 10. Deadline for Post-approval changes and marketing authorization applications

Category	Marketing Authorization Application	Post-approval Variation Application
Ordinary category	365 days	180 days
Priority category	120 days	60 days

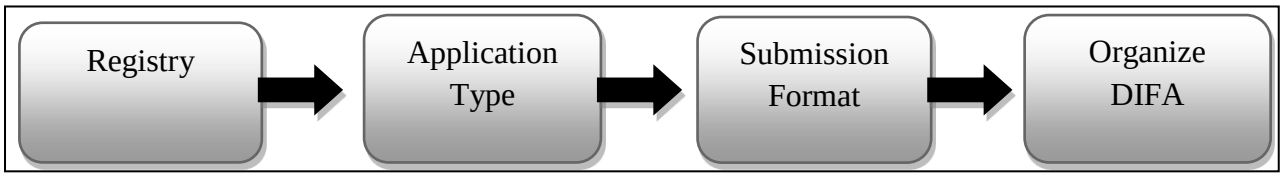

Figure 4. Steps to be taken before submitting to ANVISA

ANVISA's Guide 24/2019, along with its annexes, established the basis for the structure and content of the DIFA, incorporating the guidelines outlined in the ICH M4 guidelines specific to Brazil. This guide provides additional guidance on the preparation and submission of the DIFA and related documentation to ANVISA. Figure 4 illustrates the preceding steps leading up to the submission to ANVISA.

3.1 Registry

During the registry process, a DIFA holder is granted access to ANVISA's systems and is required to designate an authorized user. The DIFA holder is defined as a "company that possesses knowledge of the entire API manufacturing process and exercises supervision over the creation of the API, starting from the introduction of the starting material," as stated in Resolution – RDC no 359/2020. ANVISA recommends that non-Brazilian corporations appoint an Authorized Company as the DIFA holder, simplifying the compliance with regulations. Documents submitted by entities other than the DIFA holder, including those with confidentiality restrictions from starting material manufacturers or intermediaries, will not be accepted.

How to register?

The registration process varies depending on whether the DIFA holder (or Representative Company) is legally established in Brazil, holding a CNPJ (Brazilian Corporate Taxpayer Registration number).

1. If you possess a CNPJ number, please input it in the Cadastramento de Empresa (Registry System).
2. If you do not have a CNPJ number, please complete the Registry Form, sign it, and send it via email to difa.holder@anvisa.gov.br with the subject [Registry]. Upon successful registration, you will be provided with a DIFA Holder Number (DHN) and Authorized User Number (AUN). It is crucial to maintain accurate information regarding authorized users, as ANVISA can only communicate with them. Failure to acknowledge ANVISA's communication may result in application denial. Each DIFA owner and authorized user must adhere to the Registry Procedure. The Letter of Authorization, if necessary, will be included as Annex 1 with the Application Form in the future.

3.2 Application Type

Before registering in the Submission System, the DIFA holder needs to select an application type from the available options listed under CADIFA Related Applications. This choice will determine the specific submission procedures and required documentation. CADIFA-related applications fall under the "Medicine" category in ANVISA and consist of a code, description, and checklist. Each submission will be assigned a unique Submission Number, and upon filing the initial application, a Reference Number (DIFA Reference Number) will be generated.

3.3 Initial Application

There are three available choices for submitting the Initial Application:

a) An Associated CADIFA Application

b) Expression of Interest

c) A Standalone CADIFA Application. The application will be assigned a unique reference number.

a) An Associated CADIFA Application: When submitting a CADIFA along with a Drug Product Marketing Authorization or post-approval change application, it is essential to include Modules 1, 2, and 3. Once the submission is completed, the Marketing Authorization Holder must receive the DIFA Reference Number and a letter granting permission to utilize the CADIFA for the analysis of the drug product marketing authorization or post-approval change application. Failure to inform the MAH about the DIFA Reference Number by submitting the "CADIFA Process Notification" codes 11721 (registration) and 11722 (post-approval change) will result in the associated CADIFA application being closed without further investigation.

b) An Expression of Interest: To obtain a CADIFA through a stand-alone process, the DIFA holder is required to complete a specific form, which is not yet associated with a drug product marketing authorization or post-approval change application. Initially, only the Application Form needs to be submitted.

c) A Standalone CADIFA Application: Whenever requested by ANVISA, the necessary documents for a Standalone CADIFA Application must be provided, either in response to a public invitation issued by ANVISA's Board of Directors or upon approval of an Expression of Interest (Dicol). The submission must include all three modules: Module 1, Module 2, and Module 3. If the submission is not specifically requested by ANVISA, the Standalone CADIFA Application will not be reviewed and will be closed. Once the CADIFA is approved, the Standalone DIFA can be used to support a drug product marketing authorization or post-approval change application. During the analysis of the drug product marketing authorization or post-approval change application, the DIFA holder only needs to provide the Marketing Authorization Holder (MAH) with the DIFA Reference Number (process number)

and a letter authorizing its use. In this manual, the term "CADIFA Application" refers to both a Standalone CADIFA Application and an Associated CADIFA Application. Table 11 provides guidance on when to submit an initial application.

Table 11. When to submit an initial application

S.No.	Application Type	When to apply	What documents
1.	Associated CADIFA Application	The CADIFA can be linked to a marketing authorization or post-approval change application.	M1+ M2+ M3
2.	Expression of Interest	A marketing authorization or post-approval change application is not required for the CADIFA to be referenced.	Application Form
3.	Standalone CADIFA Application	Upon approval of the Expression of Interest or a public invitation issued by ANVISA's Board of Directors (Dicol).	M1+ M2+ M3

M1- Module 1
M2- Module 2
M3- Module 3

3.4 Similar DIFA

In certain circumstances, such as when a change is not feasible or the holder desires multiple CADIFAs for different manufacturing conditions or quality characteristics, the DIFA holder may seek to apply for an additional CADIFA for the same API. This could be to cover an alternative manufacturing process, manufacturing site, or grade. To streamline and expedite the evaluation process, this new CADIFA may be linked to another DIFA, whether it has already been approved or is still pending assessment. The term "Original DIFA" is used to refer to this initial DIFA. Instructions on how to address this situation can be found in Module 1: Administrative Information of the Application Form.

Module 1: Administrative Information:

Both applications must fulfill certain criteria:

- The API must be produced using the same method, whether it's extraction from botanical material, synthesis, traditional fermentation, or semi-synthesis.
- The application should include the DCB name and number, as well as the CAS number.
- The DIFA holder must remain the same or be part of the same group.
- The manufacturers involved should also remain the same.

When submitting a Similar DIFA, it should be a comprehensive application and cannot simply refer to or rely on the original DIFA. Regardless of the information contained in the original DIFA, the Similar DIFA must include complete technical documentation in accordance with the prevailing regulations. The Similar DIFA should also align with the most up-to-date technical standards, such as those outlined in ICHQ11, ICH M7, and Annex I of RDC no. 359/2020. Both DIFAs will need to be independently updated during their respective life cycles to meet the requirements stipulated in Resolution - RDC number 359/2020.

Change Application

Once the CADIFA has been granted, it becomes the responsibility of the DIFA holder to manage its lifecycle by submitting Change Applications to ensure its currency. These change applications must comply with the requirements stated in Annex II of Resolution RDC number 359/2020 and should be linked to the DIFA Reference Number. The changes must follow the predefined list of change codes provided in the CADIFA Related Applications List. The continuous management of the DIFA's lifecycle is crucial for maintaining its validity, as there is no specific renewal procedure for CADIFA. For any modifications that are considered minor and are not listed in Annex II of Resolution RDC number 359/2020, they should be submitted as a "Minor by Default" application type. Module 1, along with Module 3 if applicable, constitute the Change Application. If the Change Application affects a specific section of Module 3, an updated version of that section must be included. The supporting document required by the amendment mentioned in Annex II of Resolution RDC number 359/2020 should be submitted as per Section 1.7.4 of Module 1. Regarding modifications indicated by a blank "docs" column or changes classified as "Minor by Default," appropriate supporting documentation should be provided, considering the nature and complexity of the change. This documentation should cover the DIFA sections directly affected by the change and any additional research necessary to support the change in the relevant parts of the DIFA.

Grouped Changes

When multiple changes are interconnected or arise from other changes, it is recommended to consolidate them into a single change application. In such cases, the most restrictive reporting category should be chosen to determine the risk classification and implementation type for the change. The classification of change risks is detailed in Table 12.

When multiple changes fall into the stricter category, ANVISA recommends following a specific sequence in selecting the submission code. Various factors need to be considered, including API quality control, container closure system/storage condition/shelf life or retest time, production, and change management protocol/design space. ANVISA will make a unified decision for bundled changes. However, if the DIFA holder wishes to apply each change individually, they must be submitted separately since they are unrelated. It is important to

note that once ANVISA grants permission or the assessment period has elapsed, a modification that involves a yearly notification or an urgent notification combined with a minor or major change cannot be implemented.

Table 12. Classification of change risk

Higher Risk ↓	Modification Type	Execution Type
	Annual Notification	Immediate Implementation
	Immediate Notification	Immediate Implementation
	Minor	After approval*
	Minor by Default	After approval*
	Major	After approval**

*After 60 days without ANVISA's communication.
**Or after 180 days without ANVISA's communication.

Deficiency Letter Response

During the evaluation of a CADIFA Application or Change, ANVISA has the authority to issue a Deficiency Letter to request further information or clarification. The DIFA holder is required to respond to the Deficiency Letter within 120 days of its receipt. Only one response is allowed for each Deficiency Letter. If applicable, the response should cover all relevant aspects of Module 1, Module 2, and Module 3.

Other Application

The DIFA holder has the option to provide Additional Information to supplement previously submitted data. Additional Information refers to information that was not specifically requested and should not introduce new requirements beyond the original request. However, it is important to note that once a deficiency letter response has been submitted, it cannot be modified. The submission of Additional Information will be assessed in conjunction with the initial application (linked to it). Any submission may be subject to closure if ANVISA has not yet made a decision. The DIFA holder has the ability to request a suspension (for a maximum of two years) or withdrawal of the CADIFA. In the event that any inaccurate or incomplete information is identified following the receipt of the CADIFA, the DIFA holder is required to submit a Correction to request the necessary amendments. To request rectification, the applicant is required to submit the Application Form along with a completed Appendix 8 that outlines the incorrect information and proposes the necessary changes. If the request for rectification is denied, the applicant has the option to resubmit the request. However, it is important to note that in such cases, the request can only be submitted by a Brazilian Authorized User due to regulatory restrictions. If the technical information provided by the DIFA holder during the DIFA process leads to the partial or complete rejection of a marketing authorization or post-approval change application, the Marketing Authorization Holder (MAH) may submit a Reconsideration in the associated Marketing Authorization Application. If deemed appropriate, the MAH can refer to the technical information in their reconsideration request.

4. Submission Format

There are two available methods for submitting an application. The first option is to personally deliver the application directly to ANVISA or send it through mail, which is known as manual submission. Alternatively, applicants have the option to submit their application online using the Submission Systems, referred to as electronic submission. It is important to note that the chosen submission format, whether electronic or manual, must remain consistent for all subsequent submissions.

4.1 Manual Submission

When opting for manual application submission, the applicant must follow the guidelines outlined in Guide 24/2019 and the provided Manual. Upon submitting the required documents and media, such as a USB flash drive, to ANVISA's headquarters, a Reference Number and submission number will be assigned, initiating the regulatory transaction in the Peticionamento electronic system. The transaction is considered complete once the process is finalized within the Submission System. Subsequently, a transaction receipt containing the transaction number and fee (TFVS) exemption will be issued. The printed TFVS exemption should be included along with the following documents: I. A printed cover sheet; II. A printed application form; and III. The sealed media (USB flash drive) labelled with the company name, API, and transaction number (or Reference Number for future submissions). It should be noted that the mention of physical copies of the cover sheet in section 1.2.1, the application form in section 1.2.3, and the fee exemption in section 1.2.5 in electronic media within Module 1 is insufficient to waive the requirement for their inclusion (USB flash drive). Manual submissions should be sent to the address provided in Figure 5, which outlines ANVISA's headquarters location details.

For the application accompanied by the DIFA's Reference Number, please refer to the process for initial application submission (manual submission) in the case of a CADIFA application or expression of interest. Regarding additional submissions categorized as Change or Others, excluding response submissions, please consult the guidelines provided for change and other applications (manual submission). ANVISA will link these submissions with their respective contents upon completion and receipt of the regulatory transaction.

4.2 Electronic Submission

When opting for electronic submission, it is important to carefully follow the provided instructions. The

Submission System will serve as the platform for initiating and completing the submission process, and a receipt will be generated by the system. Each specific submission requires the submission of documents as outlined in the corresponding checklist. To proceed with the electronic submission, it is mandatory to upload at least one file for each item listed in the checklist. In cases where a document is optional or not applicable to a particular application type, the DIFA holder must attach a file providing a justification for its absence in order to proceed with the submission in the system. While the submission of Module 2 is optional in electronic submissions, if the DIFA holder chooses not to include it, they must provide an attached file explaining the reason for excluding Module 2.

Submission Receipt: Upon completing an electronic submission, a receipt will be issued containing important information such as the application type, details of authorized users, and the DIFA holder. For CADIFA applications, it is essential to include the Reference Number along with the Marketing Authorization Holder, as it serves as a reference for the subsequent post-approval or marketing authorization application for the drug product. The specific details included in the submission receipt can be found in Table 13.

Table 13. Submission Receipt

Submission	Outcome of Assessment	Decision Communication
CADIFA or Change Application	Approval	Approval Letter
	Deficiency Letter	Deficiency Letter Notification
	Rejection	Rejection Letter
ANVISA's headquarters address	À Agência Nacional de Vigilância Sanitária (ANVISA) COIFA SIA Trecho 5, Área especial 57, Lote 200 CEP: 71205-050 Brasília – DF, Brasil	

5. Approval

CADIFA will be granted, updated, or a Letter of Acceptance will be issued to confirm the acceptance of change requests, provided that the DIFA complies with Resolution - RDC no. 359/2020, which ensures appropriate API control. Significant changes or those that impact the essence of CADIFA will trigger a review of the certification. The CADIFA will be communicated exclusively to the DIFA holder's designated mailbox by ANVISA.

6. Deficiency Letter

Applications may be rejected if they are found to have insufficient information. In such cases, ANVISA reserves the right to issue a Deficiency Letter to the DIFA holder, containing a set of questions or requests for additional clarification or information. The Deficiency Letter will be sent to the designated Mailbox. The DIFA holder has a maximum of 120 calendar days from the date of opening/reading the Deficiency Letter to provide a response. Failure to submit a timely response will result in the application being rejected. The questions will be posed only once, and any subsequent inquiries would be considered an exception.

7. Rejection

If the submitted proposal fails to include the necessary documentation as mandated by Resolution - RDC number 359/2020, it will be rejected during the initial screening phase (preliminary assessment of completeness). In the event that the Deficiency Letter Response is not submitted within the specified deadline, the application will be dismissed. Following one or two rounds of inquiries, if the submission still does not comply with Resolution - RDC no 359/2020, the application will be rejected. In cases where change requests are denied, the existing version of CADIFA will remain in effect without the required updates. ANVISA will always provide a Rejection Letter to the designated mailbox, including the reasons for the rejection. The unresolved issues outlined in the Rejection Letter are expected to be addressed in any subsequent resubmissions or modified proposals made by the applicant.

8. Closure

The DIFA holder has the option to terminate any application before ANVISA reaches a final decision. In such cases, the application status will be updated to "closing upon request," and a Closure Letter will be sent to the designated mailbox of the DIFA holder.

9. Organization of DIFA

A DIFA application consists of three modules: Module 1 (Administrative Information), Module 2 (Common Technical Document Summaries), and Module 3 (Quality). In electronic submissions, Module 2 is not mandatory. ANVISA encourages the use of "General Principles" such as the "Granularity Document," "Document Pagination and Segregation," "Section Numbering Within Documents," and "Table of Contents Formatting," which align with the guidelines of ICH M4 (R4). Regarding file requirements, all files must be submitted in the portable document format (PDF), ensuring they are searchable and copyable. The maximum file size for electronic submissions is 20 MB, while for manual submissions, it is 60 MB. If a file exceeds these limits, it should be divided into multiple files to comply with the size restrictions. ANVISA supports PDF documents created from electronic sources to maintain the quality and readability of the material. Scanned documents stored as image files may hinder reviewers' ability to search for specific information or copy text, making them more challenging to evaluate. Therefore, scanning should be avoided whenever possible. PDF files should not have any security

restrictions or password protection. It is recommended to modify the security options to allow printing, registry changes, adding or updating notes and form fields, as well as selecting and copying text and artwork. For detailed information on the required documents in the administrative information section of Module 1, refer to Table 14.

Module 1: Administrative Information

Table 14. Documents in the administrative information section of Module 1

Module 1				**Applications**			
Section				**Initial Application**	**Change**	**Response***	**Others***
1.1	Table of Contents			(M)(E)		O	
1.2	Administrative Information	1.2.1	Cover Sheet	(M)		NA	
		1.2.2	Justification	O		NA	O
		1.2.3	Application Form	(M)(E)		NA	(E)
		1.2.4	Response	NA		E)	NA
		1.2.5	TFVS Payment Receipt				
		1.2.6	NA				
		1.2.7					
		1.2.8					
1.3	Communication with ANVISA	1.3.1	Meeting Minutes				O
		1.3.2	ANVISA's answers by email due to a DIFA Holder's question				
		1.3.3	Official response letter to inquires sent to the Agency				
		1.3.4	NA				
		1.3.5					
1.4	Other Administrative Information		O				
1.5	NA						
1.6	API Information	1.6.1	NA				
		1.6.2					
		1.6.3					
		1.6.4					
		1.6.5	International Regulatory Information		O		
1.7	Change, Response and Other Applications	1.7.1	NA				
		1.7.2					
		1.7.3	NA				
		1.7.4	Supporting Documentation	NA	(M)(E)	O	
		1.7.5	NA				

Module 2: Quality Overall Summary

The comprehensive quality report of the API should be included in Module 2 (2.3.S) of the DIFA application, following the format, organization, and granularity specified in ICH M4Q (R1). Module 2 sections are only required for manual submissions; for electronic submissions, Module 2 (2.3.S) is not mandatory. In case the DIFA holder decides not to submit Module 2 (2.3.S) for electronic submissions, they must provide a supporting file that explains their choice, as the Submission System mandates the upload of at least one file per Module.(7) Table 15 provides an overview of the section and documentation requirements for Module 2.

Table 15. overview of the section and documentation requirements for Module 2

Module 2				**Applications**			
Section				**Initial Application**	**Change**	**Response**	**Others**
2.1	Table of Contents (Modules 2-3)			(M)	NA		
2.2	Introduction			NA			
2.3	Quality Overall Summary	2.3. S	Active Pharmaceutical Ingredient	(M)			
M – Mandatory only for Manual Submission; O – Optional for both types of protocol; and NA – Not applicable for both types of protocol.							

Module 3: Quality:

Table 16 provides a detailed description of the necessary sections and documents for Module 3.

Table 16. Sections and documents for Module 3

Module 3		
Section		
S.1	General Information	
	S.1.1	Nomenclature
	S.1.2	Structure
	S.1.3	General Properties
S.2	Manufacture	
	S.2.1	Manufacture(s)
	S.2.2	Description of Process and Controls
	S.2.3	Control of Materials
	S.2.4	Control of Critical Steps
	S.2.5	Process Validation
	S.2.6	Manufacturing Process Development
S.3	Characterization	
	S.3.1	Elucidation of structure
	S.3.2	Impurities
S.4	Control of Drug Substance	
	S.4.1	Specification
	S.4.2	Analytical procedures
	S.4.3	Validation of Analytical procedures
	S.4.4	Batch Analysis
	S.4.5	Justification of Specification
S.5	Reference Standard or Materials	
S.6	Container Closure	
S.7	Stability	
	S.7.1	Stability Summary and Conclusion
	S.7.2	Post Approval Stability Protocol
	S.7.3	Stability Data

10. Conclusion

This article mainly consists of the detailed information about the Brazil related the registration procedure. This article deals with Country specific CMC requirement, Average approval time, structure of registration dossier, ANVISA GMP inspection details etc. This article is helpful for understanding various requirements related to the local testing and the ANVISA review process.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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