RESEARCH PAPER

Regulatory Perspectives on API Registration in the United States and Brazil: A Review of DMF and DIFA/CADIFA Systems

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ABSTRACT
Drug Master Files (DMFs) are submissions to Regulatory Authorities that include detailed information on the manufacturing, quality control, and stability of Active Pharmaceutical Ingredients (API). This study reviews the regulatory requirements, filing, and approval process for DMFs in the USA and Brazilian markets. In the USA, the DMF submission should be made electronically in eCTD format via the Electronic Submission Gateway (ESG). Type II DMF holders are required to pay a one-time Generic Drug User Fees Amendment (GDUFA) DMF fee. Upon Payment of DMF fees, the US FDA conducts a Completeness Assessment (CA). US FDA must complete 90% of the initial CA evaluation within 60 days of the DMF submission date or DMF fee payment, whichever is later. If the DMF passes the CA, the FDA will post the DMF number publicly on its website. When the authorized party includes a copy of the Letter of authorization from the DMF holder in an application or another DMF, the FDA can assess the technical data contained in DMFs. In Brazil, DIFA (API Dossier) is submitted in CTD format through ANVISA's Solicita system. If the submitted DIFA meets the requirements of Resolution RDC 359/2020, then ANVISA will issue CADIFA (Letter of Suitability of the API Dossier). There is no fee for DIFA submission. Application in the ordinary category of CADIFA is evaluated in 180 days for post-approval changes and 365 days for marketing authorization. In conclusion, the study examined the feasibility and stringency in terms of cost, documents requirements, language requirements, review timeline, submission pathway and market potential between DMF submission in the USA and CADIFA submission in Brazil.

Keywords: DMF, US FDA, ANVISA, CADIFA, Regulatory requirements
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1. INTRODUCTION

The term "active pharmaceutical ingredients" refers to any material added to a pharmaceutical formulation that, when taken by a patient, functions as an active ingredient and may have a pharmacological effect or another direct impact on the diagnosis, treatment, or prevention of disease, as well as on the structure and operation of the human body. A Drug Master File is a document submitted by a pharmaceutical manufacturer to the Regulatory Agencies that contains specific, potentially confidential data of the equipment, facilities, or materials used in the production, processing, packing, and storage of pharmaceuticals for human use. [1,2]

The Drug Master File is a crucial regulatory document in the United States, overseen by the U.S. Food and Drug Administration (FDA). This file encompasses details concerning the production, handling, packaging and storage of Active Pharmaceutical Ingredients (API). Submission of a DMF is made at the holder's discretion and is not mandated by the FDA. The information in the DMF can be referenced by applications like ANDA, NDA, INDA, or another DMF. The DMF's primary goal is to give the FDA confidential information so they may evaluate the API's safety, quality, and efficacy during the drug approval process.[3]

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After May 5, 2017, every DMF submission in the USA has to be made electronically in eCTD Format via Electronic Submission Gateway (ESG). DMF application is not independently reviewed or approved by the US FDA. Rather, the FDA solely evaluates the technical content in DMF when reviewing applications that make reference to it. When an authorized party submits a copy of the DMF holder's Letter of Authorization (LOA) with the applications (NDA, ANDA, BLA, etc.), the FDA will proceed with its DMF review. Under the Generic Drug User Fee Amendment (GDUFA), Type II API DMF will have to pay one-time DMF fees and will be subjected to Completeness Assessment (CA) upon payment of DMF fees. However, a full evaluation won't take place until an application refers to DMF 4, 5, 6

In Brazil, the API dossier is referred to as DIFA (Dossiê de Insumo Farmacêutico Ativo). DIFA is a collection of quality and administrative documents for an active pharmaceutical ingredient. If the DIFA meets the standards outlined in the RDC 359/2020 rules, ANVISA will issue a certificate known as CADIFA (Active Pharmaceutical Dossier Adequacy Letter), confirming the DIFA's final approval. CADIFA serves as evidence that the specifications and tests conducted are suitable for ensuring API's quality.[7]

The assessment of CADIFA is not intended to confirm GMP compliance, even though the manufacturer is responsible for making sure the API is manufactured as per Good Manufacturing Practice (GMP). Thus, CADIFA is not a substitute for a GMP certificate. For market authorization or post-approval application approval, both a valid CADIFA and GMP certificate are required. DIFA is submitted electronically in CTD format via ANVISA's Solicita system.[8]

2. REQUIREMENT FOR US DMF COMPILATION

- A thorough checklist of data needed, based on submission strategy as per current requirements prevalent in certain countries or regions, must be available before starting with DMF compilation.
- Using the DMF checklist, request required documents from Cross-Functional Teams (CFTs).
- Check the sufficiency of the required documents.
- With the help of documents received from CFTs, start with DMF compilation.
- The DMF should be in English.
- DMF compilation will be done in ICH M4-CTD format.
- Modules 1, 2, and 3 must be included in DMF.
- The compiled DMF section must be reviewed for appropriateness.
- Convert CTD to eCTD format by using a software tool.[9]

2.1 Format for US DMF

- Each DMF submission must include a transmittal letter, administrative and technical data.
- A cover letter should be given for every submission to aid with document processing.
- All submissions must be made in English. Applicant will require a certified English translation if any of the content is in another language.
- DMF needs to be prepared in eCTD format as per US FDA requirements. The materials that have been scanned must be searchable and readable.
- Provide original copy of DMF.
- Reference copy of the submission for the record should be kept by the DMF holder & their agents.
- Every page of DMF must have a unique number and be dated.
- Choosing the proper centre (CDER or CBER) when submitting through ESG is essential for proper routing of DMF.[10]

2.2 Transmittal letter

The following details should be included in the initial DMF:

- DMF Identification: Original, type of DMF and its subject.
- Identification of the application to which DMF is intended to support.

Name and address of the following:
(1) Holder of DMF

(2) Corporate Headquarters

(3) Manufacturing/processing facility

(4) Contact for FDA correspondence

(5) Agent(s), if there is any.

- Specific responsibility of each person mentioned above.
- Statement of commitment.
  - DMF holder, authorized agent or representative's signature.
  - A certified statement from the holder confirming the DMFs currentness.
- Signer's name and title.[11]

2.3 Administrative information

- Name, address, corporate headquarters, processing/manufacturing facility, DMF holder's contact number, fax number, and email address, as well as the person to contact for FDA correspondence.
- Statement of Commitment

- List of referenced applications.[12]

2.4 Technical information

Module 1 should include administrative information relevant to DMF, Module 2 should give a summary, and Module 3 should cover detailed information on drug substances, including all sections 2.3.S and 3.2.S.[13]

CTD modules, sections, and titles are shown in Figure 1.

Module	*Section*	*Title*
Module 1 Administrative Information and Prescribing Information	1.1	Table of Contents of the Submission Including Module 1
	1.2	Documents Specific to Each Region (for example, Cover letter, application forms, prescribing information)
	1.3	Administrative Information
	1.3.1	Contact/sponsor/applicant information
	1.3.1.1	Change of address or corporate name
	1.3.1.2	Change in contact/agent
	1.3.3	Debarment Certification
	1.4	References
	1.4.1	Letter of Authorization
	1.4.3	List of authorized persons to incorporate by reference.
Module 2 Common Technical Document Summaries	2.1	Common Technical Document Table of Contents (Modules 2-5)
	2.2	CTD Introduction
	2.3	Quality Overall Summary
Module 3 Quality	3.1	Table of Contents of Module 3
	3.2	Body of Data
	3.2. S	DRUG SUBSTANCE (NAME, MANUFACTURER)
	3.2. S.1	General Information (name, manufacturer)
	3.2. S.1.1	Nomenclature (name, manufacturer)
	3.2. S.1.2	Structure (name, manufacturer)
	3.2. S.1.3	General Properties (name, manufacturer)
	3.2. S.2	Manufacture (name, manufacturer)
	3.2. S.2.1	Manufacturer(s) (name, manufacturer)
	3.2. S.2.2	Description of Manufacturing Process and Process Controls (name, manufacturer)
	3.2. S.2.3	Control of Materials (name, manufacturer)
	3.2. S.2.4	Critical Steps & Intermediates (name, manufacturer)
	3.2. S.2.5	Process Validation and/or Evaluation (name, manufacturer)
	3.2. S.2.6	Manufacturing Process Development (name, manufacturer)
	3.2. S.3	Characterization (name, manufacturer)
	3.2. S.3.1	Elucidation of Structure and other Characteristics (name, manufacturer)
	3.2. S.3.2	Impurities (name, manufacturer)
	3.2. S.4	Control of Drug Substance (name, manufacturer)
	3.2. S.4.1	Specification (name, manufacturer)
	3.2. S.4.2	Analytical Procedures (name, manufacturer)
	3.2. S.4.3	Analytical Validation (name, manufacturer)
	3.2. S.4.4	Batch Analyses (name, manufacturer)
	3.2. S.4.5	Specification Justification (name, manufacturer)
	3.2. S.5	Reference Standards or Materials (name, manufacturer)
	3.2. S.6	Container Closure System (name, manufacturer)
	3.2. S.7	Stability (name, manufacturer)
	3.2. S.7.1	Stability Summary and Conclusions (name, manufacturer)
	3.2. S.7.2	Post-approval Stability Protocol and Stability Commitment (name, manufacturer)
	3.2. S.7.3	Stability Data (name, manufacturer)
	3.2	Literature References

Fig.1: CTD Table of Contents and Headings

2.5 Generic Drug User Fee Amendment (GDUFA) and Completeness Assessment (CA)

As of October 1, 2012, GDUFA requires DMF holders of Type II DMF to pay a one-time fee when the DMF is first referenced in a generic drug application submitted to the US FDA. On September 30, 2022, GDUFA was renewed to GDUFA III, which will remain in effect from Oct 1, 2022, to Sept 30, 2027. GDUFA fee for the financial year 2025 is $ 95,084.[14,15,16]

2.6 Submitting DMFs in eCTD format

Submission of DMF in eCTD format includes the following steps

a) Obtaining a pre-assigned application number

- To fill in the US Regional.xml, the DMF holder must get a pre-assigned number before submitting the DMF.
- CDER NextGen Portal is used to submit requests for a pre-assigned number.[17]

b) Convert DMF to eCTD format

- DMF has to be converted to eCTD format using software tools (like Lorenz docuBridge)
- All the sections of modules 1,2 and 3 must be submitted for new electronic DMFs.[18]

c) Submission via Electronic Submission Gateway (ESG) to the US FDA

- Submission must be made through ESG if it is 10 gigabytes or less.
- Submissions larger than 10 gigabytes can be sent via physical media (such as a DVD or USB drive) or ESG.
- The eCTD file must be checked and validated before submission to prevent submission errors.[19]

2.7 US DMF Completeness Assessment Review Process

- Type II DMF for which GDUFA DMF fees are paid will undergo a Completeness Assessment (CA) by using the Completeness Assessment Checklist.
- The Completeness Assessment does not substitute for the full scientific assessment, which evaluates whether the data in the DMF are adequate to support regulatory action on ANDA.
- DMF submission must be accompanied by a Generic Drug User Fee Cover Sheet (Form FDA 3794).
- Centre for Drug Evaluation and Research (CDER) will conduct Completeness Assessment Review. 90% of the review must be completed within 60 days from either the DMF submission date or the date of the DMF fee payment, whichever is later.
- If the DMF meet the requirement as per the Completeness Assessment Checklist, then the DMF will be listed as "Available for Reference" on the FDA website.
- If any deficiency is found during the assessment, then the FDA will issue a GDUFA Incompleteness Letter to the DMF holder, which has to be responded to within 30 days. [20]

The flowchart for the US DMF CA Review Process is shown in Figure 2.

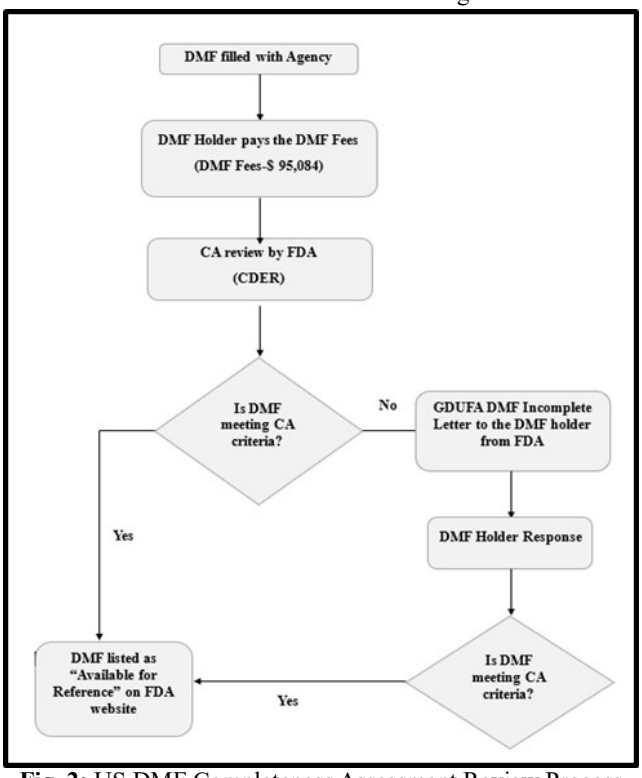

Fig. 2: US DMF Completeness Assessment Review Process

2.8 FDA Review and Approval

The FDA reviews the DMF in 2 steps as given below:

a) Administrative Review

If the administrative information in the DMF is found appropriate, then the FDA will issue an acknowledgement letter to the DMF holder (and agent, if applicable). It includes the DMF number, title, type, and holder's name as given in the cover letter. If any of the administrative information is not found accurately, the FDA contacts the DMF holder to request the required details. The DMF will not be available for technical review until the administrative error is solved and it is referenced in an application or another DMF.

b) Technical Review

When the authorized party submits the LOA of the DMF holder in their application or another DMF, the FDA will conduct a detailed assessment of the referenced technical data. During the assessment process, if there is a requirement for any extra information or if there is any mistake in the technical data, then the FDA will contact the DMF holder or their agent to provide the missing data.[21]

2.9 US DMF Amendment

If a DMF holder makes any changes or updates to the existing DMF after its first submission, an amendment must be submitted to the US FDA. For submitting an amendment, Module 1 must include a Cover letter, administrative page, FDA form 3938, quality information amendment (Summary of changes), and Statement of Commitment, and Module 3 must include updated

sections. The affected party must be notified of any amendment to the DMF. An amendment can be either administrative or quality-related.

a) Administrative amendments
Some of the administrative amendments include:

Name change, acquisitions, or ownership transfer
DMF holders must submit an administrative modification to each DMF they own to notify them of any name change. Name changes may be the result of a simple name change or acquisition, or transfer of ownership of the DMF holder to another company. In case of ownership transfer, the DMF holder must submit an acceptance notification, while the previous DMF holder must provide a transfer notification.

Change to DMF subject.
Any modification in the subject or title of the DMF must be submitted as an administrative change. If there is a change in technical content, such as the grade of API in DMF, then the quality amendment must be submitted along with the title change.

Change to DMF type
If there is any change in DMF type, then an administrative amendment must be submitted. If the type change requires updating of technical data, then the DMF holder must submit a quality amendment with the necessary modification.

b) Quality Amendment
Any modification to technical data must be included in the quality amendment. Some examples of quality amendments are test procedure changes, stability data updates, changes in starting material information, etc.[22]

Annual Report
- An annual report from the holder is required on the anniversary of the initial filing.
- It has to specify any changes and additional data included in DMF since the last yearly report on the DMF's matter.
- Cover letter, administrative page, List of authorized persons, incorporate references, and Form 3938 should be submitted along with the annual report.[23]

DMF Closure
- A DMF can be closed if the DMF holder requests or if the FDA determines that it is not up to date.
- To close a DMF, the holder must submit an administrative amendment requesting closure. This request should include a statement confirming that all authorized parties have been notified of the closure.
- A new DMF can be submitted by the holder to replace the closed one, referencing the closed DMF number in the updated submission.[24]

3. Regulations for CADIFA (API) in the Brazilian Market

The Guidelines governing CADIFA in Brazil are:

RDC 359/2020: This Resolution establishes DIFA and CADIFA.

RDA 362/2020: This resolution establishes an inspection program for global organizations that produce API and specifies requirements for Good Manufacturing Practice (GMP) certification.

Normative Instruction (NI) 289/2024: This defines the standards for the optimal analysis process, which is based on RDC 741/2022. The evaluation carried out by the Equivalent Foreign Regulatory Authority (AREE in Portuguese) is used to analyse registration and post-approval variation applications for Pharmaceuticals, biological products, vaccines, and APIs in Brazil.[25,26]

3.1 Types of CADIFA application

a) Initial application

Can be submitted through one of the three available options shown in Table 1:

Table 1. Types of Initial Applications

Sl. No.	Type of applications	When can it be applied
1.	Associated CADIFA application	Submitted when CADIFA is associated with the MA or PAC application
2.	Expression of interest	No MA or PAC application demanding CADIFA
3.	Standalone CADIFA application	Can be submitted after the expression of interest or public invitation issued by ANVISA's Board of Directors (Dicol)

3.2 Similar DIFA
In some cases, the DIFA holder can seek a second CADIFA for the same API, such as when a change request is not practical or when a separate CADIFA is required for different manufacturing conditions or quality attributes (e.g., an alternative manufacturing process, site, or grade). This is referenced as Similar DIFA. A similar DIFA must be a complete submission; hence, it cannot reference the original DIFA to replace sections of the dossier. It must include full technical documentation aligned with the latest technical standards.

b) Change application
If the DMF Holder wants to incorporate any changes as a part of DIFA lifecycle management after CADIFA is granted, then the DMF holder must submit a change application. Module 1 and, if applicable, Module 3 must be included in the change application. An updated version of the affected section of Module 3 should be submitted

each time the Change affects it. It is required to classify and list every change separately in the comparative table.

c) Deficiency Letter Response
ANVISA may issue a Deficiency letter requesting additional data or clarification during the evaluation of CADIFA or a change application. The DIFA holder must respond within 120 days of accessing the letter in the Solicita System. If the CADIFA application is associated with the medication of rare diseases, then a response must be submitted within 30 days.

d) Other Application
Other applications include additional information submission to complement previously provided data, Closure requests, CADIFA withdrawal or suspension, and Reconsideration.[27]

Organization of DIFA

Module 1: Administrative Information
Module 1 consists of administrative data mandated by Resolution RDC nº 359/2020.

Module 2: Quality Overall Summary
Module 2 must include a Quality Overall Summary. This section is optional for electronic submission**.**

Module 3: Quality
Module 3 should include documents detailing quality information following the Resolution RDC nº 259/2020.

3.3 CADIFA Submission and Approval Process

- The Solicita System is a web-based platform by ANVISA, which will be used for CADIFA-related applications and communication. It serves as a channel for sharing information between ANVISA and DIFA holders.
- Through a registry procedure, DIFA holders gain access to the Solicita system. During this stage, the DIFA holder must appoint an authorized user. Authorized users act on behalf of the DIFA holder within ANISA's Solicita system. In case the holder has multiple manufacturing sites in multiple countries, then an Authorized User can be assigned for each site. The Authorized User can also be appointed as a Regulatory User, granting access to the entire content of documents filed with the ANVISA in the Solicita system, including the documents filed by another authorized user. Once the Registry process is complete, an Authorized User Number (AUN) and DIFA Holder Number (DHN) will be assigned.
- Companies with CNPJ (Brazilian Corporate Taxpayer Registration number) must proceed to the Registry system for online registration (Cadastramento de Empresa).
- Companies without CNPJ should fill the registry form, sign the form, and then send it to difa.holder@anvisa.gov.br and should give the subject as [Registry].
- After the completion of registration, the holder must select the application type and fill out the application form.
- DIFA holder must submit the CTD format through the Solicita system.
- ANVISA's evaluation timeline for the Ordinary category, priority category, and rare disease is shown in Table 2.

Table 2. ANVISA evaluation timelines

Category	Marketing authorization application	Post-approval variation application
Ordinary category	365 days	180 days
Priority category	120 days	60 days
Treatment of rare disease	60 days (first manifestation) 45 days (deficiency letter response)	

- If DIFA meets the requirements of Resolution RDC no. 359/2020, then ANVISA will issue a CADIFA certificate.
- If there is any deficiency, a Deficiency Letter will be issued by ANVISA to which the DIFA holder must respond within 120 days.[28,29]

ANVISA's regulatory process for CADIFA Certification is shown in Figure 3.

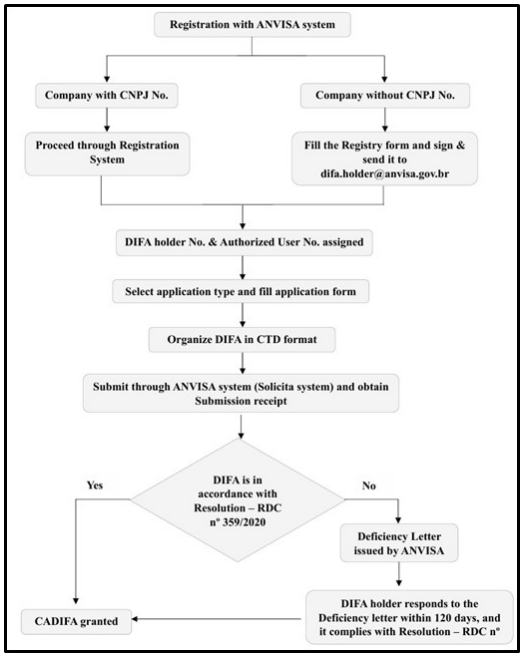

Fig. 3: Flowchart of CADIFA Submission and Approval Process

3.4 GMP Certification

ANVISA's GMP Certificate of API manufacturer is a prerequisite for market authorization.

Both a valid CADIFA and GMP certification are needed to approve an associated MA or PAC application. RDC 362/2020 institutes the program of inspection for the international establishment of API and sets the requirements for GMP certification.

A GMP certificate is granted by one of the following methods:

- Evaluation of the inspection report given by the regulatory authority that ANVISA considered comparable in terms of procedure and controls used to demonstrate GMP.
- Reviewing the documents and conducting a risk assessment that will support certificate issuance.
- Assessing the inspection report given by the agency, followed by on-site inspection, the assessment should consider whether the inspection was prompted by risk analysis or the absence of a prior inspection report.[30]
- The GMP Certification granting process is shown in Figure 4.

Fig.4: GMP Certification Granting Process

3.5 Reliance Procedure

Reliance Procedure means if an API has already been evaluated and approved by recognized authorities (such as EMA, FDA, etc.) ANVISA may use that assessment to streamline the CADIFA approval process. Normative

Instruction 289/2024 defines the standard for the optimised analysis procedure.

Reliance Procedure includes below steps:

- For the API that is already approved in ANVISA-designated Equivalent Foreign Regulatory Authorities (EFRA), the Reliance mechanism is applicable.
- Submission must include API checklist (Annex III, NI 289/2024), EFRA-approved documents, a Comparison of Brazil vs. EFRA-evaluated documents, and a report showing that API is equivalent to EFRA-approved API.
- ANVISA will conduct an administrative evaluation for completeness.
- If the administrative documents are found complete, then ANVISA will conduct an optimized review based on EFRA evaluation.
- If any additional information is required, ANVISA will request the DIFA holder.
- If all the requirements are met, then ANVISA will issue CADIFA.[31]

4. COMPARISON BETWEEN US DMF AND CADIFA

A comparison between the US Drug Master File (DMF) and Brazil's CADIFA is shown in Table 3.

Table 3. Comparison of DMF regulations between the USA and Brazil

Parameters	USA	Brazil
Definition	DMFs are submitted to the FDA to give sensitive, detailed information on facilities, processes, or articles used in the manufacturing, packing, and storing of human drug products.	DIFA (API dossier) is the collection of quality and administrative documents for an active pharmaceutical ingredient that should be submitted for a CADIFA application. CADIFA (Letter of suitability of API) is the certificate that confirms DIFA's compliance with Resolution RDC 359/2020 and its approval.
Regulatory Authority	US FDA	ANVISA
Types of DMF	Four types of DMF: Type-II, Type-III, Type-IV, Type-V	Three types of CADIFA applications: Associated CADIFA application, Expression of Interest, and Standalone CADIFA application.
Applicant part (AP)/ Restricted part (RP)	AP & RP are not separated. Consolidated DMF is submitted to the authority.	AP is submitted to the customer, which is then forwarded to ANVISA. RP is directly submitted to ANVISA as a supporting document for the given applicant's DMF number.
Submission Format	eCTD	CTD
CTD Modules	Modules 1, 2 and 3 are submitted Executed BMR is mandatory.	Modules 1, 2 (optional for electronic Submission) and 3 are submitted. Executed BMR is not mandatory.
Language	English	Portuguese/English
Fees	As per GDUFA, there is a fee for a Type II DMF submission. There are no fees for other types of DMF submissions.	There is no fee to obtain a CADIFA.
Letter of authorization	Required	Required
Content Requirement	Module 1 must include a Cover letter, a Generic Drug User Fee cover sheet, a Debarment certificate, an administrative page, a change of agent, and an environmental declaration. Module 2 includes Quality Overall Summary. Module 3 includes all the sections in CTD format.	Module 1 must include a Cover letter and application form. Module 2 includes a Quality Overall Summary (Optional for electronic submission) Module 3 includes all the sections in CTD format.
Submission System	Electronic submission through the	Electronic submission is done through

	FDA's Electronic Submission Gateway or on physical media (CD/DVD)	the Solicita system (ANVISA's submission system)
Review Timeline	FDA must complete 90% of initial CA within 60 days.	Ordinary Category: MAA: 365 days PAC: 120 days

5. CONCLUSION

This review provides a comprehensive understanding of the US DMF submission procedure, including compilation in CTD format, electronic submission via Electronic Submission Gateway, Letter of authorization, GDUFA fees, Completeness assessment review, amendments, annual reports, and DMF closure. Similarly, the study explored the CADIFA filing process with ANVISA, which covered application types, DIFA organization, submission via the Solicita system, GMP certification, and Reliance procedure. A comparative analysis of both regulatory pathways highlighted key differences between US DMF and CADIFA. ANVISA offers a more cost-effective and flexible approach, as there is no submission fee and the documentation requirements are less stringent. In the case of language, the US FDA requires the submission in English, while ANVISA accepts documents in Portuguese and English, which can be a challenge for non-Portuguese-speaking API manufacturers. The FDA completes 90% of CA review within 60 days, whereas ANVISA takes 365 days for review of MAA and 120 days for PAC application. The feasibility of DMF submission with the US FDA and CADIFA submission with ANVISA depends on various factors like cost, regulatory complexity, language requirements, and market potential. Thus, the study concluded that ANVISA is more feasible in terms of cost and administrative simplicity, especially for local or regional markets. However, the FDA will be a better choice for global recognition and faster approval, though it is more demanding. FDA's approach to DMF submission and assessment is more detailed, demanding, and globally harmonized, making it more stringent when compared to ANVISA.

LIST OF ABBREVIATIONS

ANDA: Abbreviated New Drug Application; **ANVISA:** Agência Nacional de Vigilância Sanitária; **API:** Active Pharmaceutical Ingredient; **CADIFA:** Active Pharmaceutical Ingredient Dossier Adequacy Letter; **CTD:** Common Technical Document; **DIFA:** Active pharmaceutical Ingredient Dossier; **DMF:** Drug Master File; **eCTD:** Electronic Common Technical Document; **ESG:** Electronic Submission Gateway; **GDUFA:** Generic Drug User Fee Amendment; **GMP:** Good Manufacturing Practice; **ICH:** International Council for Harmonisation; **LOA:** Letter of Authorization; **MA:** Market Authorization; **NDA:** New Drug Application; **PAC:** Post Approval Changes; **USFDA:** United States Food and Drug Administration.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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