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Review Article

A Comparative Study Of Drug Master File Regulation In Brazil, Malaysia And Russia

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ABSTRACT

The burgeoning pharmaceutical market in Brazil, Russia, and Malaysia presents a compelling opportunity for drug development and access. However, navigating the intricacies of drug registration in these countries requires a thorough understanding of their regulatory frameworks, including Drug Master File (DMF) filing procedures. This research article delves into a comparative analysis of DMF requirements in Brazil, Russia, and Malaysia, exploring similarities and differences in content requirements, submission procedures, and review processes. The aim is to equip pharmaceutical companies with the necessary knowledge to navigate these regulatory landscapes effectively.

INTRODUCTION

The global pharmaceutical landscape is undergoing a significant transformation. Emerging markets like Brazil, Russia, and Malaysia are rapidly evolving as key players in drug development and access. This growth necessitates a deeper understanding of their regulatory frameworks, particularly for pharmaceutical companies seeking to register drugs in these regions. Drug Master Files (DMFs) are crucial documents submitted to regulatory agencies by manufacturers of drug substances or excipients, as outlined by the International Council for Harmonisation (ICH) Q1 guidelines. These detailed files provide critical information about the manufacturing process and quality control (QC) standards for the drug substance or excipient, allowing regulatory agencies to assess the safety, efficacy, and consistency of the final drug product. While ICH Q1 guidelines provide a foundation,

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individual countries may have additional requirements specific to their regulatory frameworks. This article explores the variations in DMF filing procedures across Brazil, Russia, and Malaysia, offering valuable insights for pharmaceutical companies seeking to expand their reach into these markets.

REGULATORY FRAMEWORK

Brazil[2]:

ANVISA (National Health Surveillance Agency) is responsible for regulating pharmaceuticals and DMFs in Brazil. ANVISA follows the International Council for Harmonisation (ICH) guidelines for DMFs, with some local variations.

Malaysia[3]:

The National Pharmaceutical Regulatory Agency (NPRA) governs the pharmaceutical sector in Malaysia. NPRA follows the ASEAN Common Technical Requirements for Drug Products (ACTD) guidelines for DMFs, which are harmonized with ICH guidelines.

Russia[4]:

The Ministry of Health of the Russian Federation oversees pharmaceutical regulations. While Russia does not have a dedicated DMF system, it allows for the submission of "dossiers" containing similar information as a DMF.

DRUG MASTER FILE REGISTRATION

1. Brazil[1,2]

The administrative document that validates a DIFA (Active Pharmaceutical Ingredient Dossier) is called a CADIFA (Letter of Suitability of the Active Pharmaceutical Ingredient Dossier). Similar terms: RDC nº 359/2020 fulfills the criteria, as do APIMF, ASMF, and DMF. In essence, it confirms that the tests included in the API's requirements are sufficient for monitoring its quality. Nevertheless, neither the quality of a particular API batch nor its substitution for a certificate of analysis are assured by a CADIFA.

The DIFA holder must submit a DIFA to ANVISA in order to get a CADIFA. A marketing permission or post-approval modification application must be submitted both before and together with the CADIFA application. The earliest possible date for submitting the CADIFA application is not indicated.

Types of application

A. Initial Application

i. Associated CADIFA Application

ii. Expression of Interest

iii. Standalone CADIFA Application

B. Change Application

C. Deficiency Letter Response

D. Other Application

Registration

DIFA holders must designate an authorized user and obtain access to the Solicita system in order to complete the registration procedure. As per Resolution - RDC nº 359/2020, a business that holds a DIFA is one that has a thorough understanding of the complete API manufacturing process and is in charge of supervising production from the point of commencing material introduction. The administrative center of the holding company or business group, which represents all of the affiliates or manufacturing locations, should be the DIFA holder. It is advised that an Authorized Company serve as the DIFA holder for non-Brazilian businesses. Documents submitted by other parties are prohibited and may only be submitted by the DIFA holder. An Authorized User has access to all regulatory data and private information on behalf of the DIFA holder in Anvisa's Solicita system. They are nominated by the Responsible Official or Legal Representative of the DIFA Holder. The number of Authorized Users is unlimited, however it's advised to have at least two. Every manufacturing facility, regardless of location, may have a single Authorized User. A user must also be classified as a Regulatory User if they require access to all papers submitted through Solicita.[3]

Content of DIFA

The content and format of the DIFA (Drug Master File) are structured according to the Common Technical Document (CTD) guidelines.

Module 1: Administrative Document

Module 2: Summary (Optional)

Module 3: Quality 3.2.S (Drug Substance part)

2. Malaysia[3,5,6]

"API refers to any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used so, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body."

Content of DMF(Drug Master File)

The content and format of the DMF (Drug Master File) are structured according to the ASEAN Common Technical Dossier (ACTD) guidelines.

Part II: Quality Document (Drug Substance part)

Procedure for submission

There are three ways in which the API information can be sent to NPRA.

Option 1: "Drug Master File (DMF) procedure"; or

Option 2: "Certificate of Suitability of the European Pharmacopoeia (CEP)"; or

Option 3: "Part II-S ACTD"

Required Information

Option 1: "Drug Master File (DMF) procedure"

- Through the online system, Part II-S (Open Part).
- To preserve the secrecy of the contents, the DMF holder must send the DMF (including the open and closed parts) to the NPRA in an electronic form (CD or DVD).
- Access Letter (LOA)
- The most recent GMP certification issued by a regulatory organization, or any other evidence of GMP compliance;

Option 2 : "Certificate of Suitability of the European Pharmacopoeia (CEP)"

- Part II-S (Open Part) over the internet platform (as determined suitable)
- A written declaration from the CEP

Option 3: "Part II-S ACTD"

- Complete information on Part II-S ACTD using the web platform.
- The most recent GMP certificate or any other paperwork attesting to GMP compliance from a regulatory organization;

Online Submission

I. The online QUEST system should be used to submit all Part II-S data.

II. Information for Part II-S must be supplied separately when:

a A final product may contain many APIs; or

b API may be produced at multiple production locations; or

c API may be produced using multiple synthesis routes.

III. There are three ways to provide information for Part II-S. See 6.2.2 section.

IV. Following the receipt of screening permission, modifications to the submission choice or the inclusion of an API manufacturer are not permitted.

3. Russia[4]

To commercially distribute an active pharmaceutical ingredient (API), the manufacturer or holder of API rights must undergo official registration of the API in Russia.

According to the laws of the Russian Federation and relevant national regulations, all APIs in Russia can be categorized into three groups:

a. Registered commercial APIs

Upon registration, APIs of this nature can be lawfully imported and distributed, with their circulation governed by Federal Law 61-FZ "On Circulation of Medicinal Drugs."

A manufacturer of a registered API has the option to engage multiple local Finished Dosage Product (FDP) manufacturers for incorporating the registered API into their production processes.

b. APIs, whose dossiers (ADMF) were approved in frames of state registration of a finished drug product (FDP)

Stringent restrictions are imposed on APIs falling within this category:

- These APIs are exclusively associated with the registered Finished Dosage Product (FDP), confined solely to the manufacturing purposes delineated in the registration dossier of that specific FDP.
- Any methods of distribution or commercial utilization of these APIs outside the quality agreements established between the API manufacturer and the Marketing Authorization Holder (MAH), referred to in Russia as the "Registration Certificate Holder," of the specific registered Finished Dosage Product (FDP) are prohibited in Russia.
- If there are contract API manufacturers involved and there are no "exclusive" production and commercial restrictions outlined in the quality agreements with the Marketing Authorization Holder(s) (MAHs) of the Finished Dosage Product(s) (FDPs), these APIs cannot be lawfully marketed in Russia beyond the "manufacturing only" constraints specified in the registration dossiers of the corresponding registered FDPs.
- When local Finished Dosage Product (FDP) manufacturing is involved, these APIs are anticipated to be included in the Russian registration certificates of the respective registered FDP(s), allowing their importation solely for the purpose of local manufacturing of the corresponding bulk drug product(s).

c. Non-registered APIs

The commercial import and marketing of these APIs are expressly forbidden in the Russian Federation.

EAEU GMP Certification

An EAEU GMP certificate for the API production facility is required in order to register a commercial API in Russia, which entails its inclusion in the state registry of medicines. Before 2021, API registration required a Russian GMP certificate; however, as of right now, the national procedure calls for an EAEU GMP certificate.

Requirements for the API dossier

The guidelines for compiling an API registration dossier are governed by Federal Law 61-FZ "On the Circulation of Medicinal Drugs." The technical components of the dossier resemble those outlined in the European Medicines Agency (EMA) , as per the regulations detailed in the EMA Guideline on Active Substance Master File Procedure.

Content of DMF

The content and format of the DMF (Drug Master File) are structured according to the Common Technical Document (CTD) guidelines.

Module 3: Quality 3.2.S (Drug Substance Part)

COMPARATIVE ANALYSIS

Table 1Comparative table of Drug Master File of Brazil, Malaysia and Russia[2,3,4]

Parameter	Brazil	Malaysia	Russia
Authority	Brazilian Health Regulatory Agency (ANVISA)	National Pharmaceutical Regulatory Agency(NPRA)	Ministry of Health (Minzdrav)
Definition of Drug Master File	CADIFA (letter of suitability of the active pharmaceutical ingredient) is the administrative instrument	The Drug Master File (DMF) is a document that	NA

	that attests the compliance of a DIFA (active pharmaceutical ingredient dossier) with the requirements of Resolution – RDC nº 359/2020. In other words, it attests that the quality of the API (Active pharmaceutical ingredient) is suitably controlled by the tests that comprise its specification.	may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more API.	
Submission name	DIFA	DMF	DMF
Types of Application	4	3	NA
Format	CTD	ACTD	CTD
Use of DMF	Marketing Authorization	New Product Registration	Finished Drug Product registration
Language	Application form: Portuguese Technical Document: English	English	Russian
Is it mandatory	No	No	No
Approved/ Disapproved by Authority	Only accepted	Only accepted	Only accepted
Review time	Ordinary: 365 days Priority: 120 days	*Reviewed only in connection with application for product registration*	4-8 months
CTD/ACTD module	Module 1 Module 2* Module 3 S	Part II S	Module 3
Applicant Part/ Restricted Part	Open part of DMF submitted to the dedicated MA. Closed part direct submitted to NPRA by API manufacturer.	Open part of DMF submitted to the dedicated PRH. Closed part direct submitted to NPRA by API manufacturer.	Open part of DMF submitted to the dedicated Registration certificate holder. Closed part direct submitted to NPRA by API manufacturer.
Agent Requirement	Required	Not required	Not required
GMP Audit	Required	NA	Required
Validity	No validity	No validity	No validity
Content of Module	Module 1: Administrative Information, Table of Content, Justification, Application form, Deficiency letter response, Meeting report, International	Part II: 2.S Substance part	Module 3: 3.2.S (Substance part)

	regulatory information, Supporting document Module 2*: Quality overall summary Module 3: 3.2.S (Substance part)		
Fees	No fees	Fees incorporated with Product registration	No fees
Updation	Updated by change application	Required	Required
Renewal	No renewal	NA	NA
Deficiency Letter	Yes	Yes	Yes
Closure or Withdrawal	Applicable	Applicable	Applicable
Reactivation	Applicable	Applicable	Applicable

CONCLUSION

The comparative study of DMF regulations in Brazil, Malaysia, and Russia underscores the importance of understanding and navigating the unique regulatory landscapes in each country. While there are commonalities in their alignment with ICH guidelines, each country presents distinct requirements and challenges that pharmaceutical manufacturers must address. Staying informed about the latest regulatory developments and ensuring compliance with local regulations are crucial for successfully bringing products to market in these growing pharmaceutical markets. By following the outlined procedures, adopting appropriate strategies, and seeking local expertise where needed, companies can effectively navigate the DMF filing process. This study provides valuable insights into the DMF submission processes and requirements in Brazil, Malaysia, and Russia, helping stakeholders in the pharmaceutical industry make informed decisions and achieve regulatory approval efficiently, ensuring the smooth flow of drug substances and excipients across borders.

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