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Assessment of Regulatory requirements and filing procedure of Drug Master File for Brazil, Europe and South Africa

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Abstract

A Drug Master File is a record that consists of detailed, correct data approximately an Active Pharmaceutical Ingredient (API) or Dosage Form of a Finished Product (FP). It is a classified document containing thorough, accurate, and up-to-date information regarding the active medicinal ingredient and medicament. A DMF is divided into two sections: (a) Open part (the Applicant's Part), which includes all of the details needed to determine the quality of a product. And (b) the Closed Part (Restricted Part). The Restricted Part (Closed Part) comprises openly undisclosed manufacturing method knowledge only given to authorized individuals. This compilation aims to offer a comparison of DMF regulatory necessities in addition to the exact data for the registration of lively pharmaceutical ingredients (API) for common drugs in various regulatory governments, including EUROPE (EDQM, EMA), BRAZIL (ANVISA), and SOUTH AFRICA (SAHPRA). This review will provide information on the differences and similarities in the DMF filing requirements in EUROPE, BRAZIL, and SOUTH AFRICA. The regulatory criteria for API registration vary by jurisdiction. Despite the existence and widespread adoption of an ICH-CTD standard format, there are also some limitations. There are a few particular requirements set provided to drug authorities along with the submission. The registration procedure is a regulatory undertaking that permits a person/organization/sponsor/innovator to get permission to participate in the regulation process for fetching marketing authorization/approval.

Keywords: Drug Master File (DMF), Regulatory Requirement, Brazil (ANVISA), Europe (EMA, EDQM), South Africa (SAHPRA).

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1. Introduction

1.1 Introduction to Drug Master File (DMF)

DMF is a report created with the valuable resource of the pharmaceutical company and submitted to the relevant regulatory authority within aspect the targeted drug market entirely at its discretion. It is a Document associated with the high-satisfactory of Drug Substances, Excipients, and Packaging substances for evaluation in reference to New Drug applications.

Application: DMF is a non-public record that carries unique data concerning facilities, procedures, or objects used within the manufacturing, covering, distilling, and maintaining of more than one human pharmaceutical. (1)

1.2 Introduction to Brazil

Brazil is the largest country in the South American region. ANVISA is the regulatory body in Brazil. ANVISA is an abbreviation for "Agencia Nacional de Vigilancia Sanitaria." This terminology was written in the Portuguese language. It means "National Health Surveillance Agency" in the English language. On 26th January 1999, it was written as "Brazilian Health Surveillance Agency". As a result, it does not have a long history. According to ANVISA, some small countries near Brazil have adhered to the ANVISA rules. ANVISA is the Brazilian regulatory group concerned with supervising and approving food items, beauty products, tobacco, pharmaceutical drugs, healthcare, and medical equipment. (2)

Before the new policy for API registration [RDC (Resolution of the Collegiate Board of Directors), 57/2009], multiple API- related guidelines were used for

API filing. Later on, a new policy, RDC 359/2020, was implemented for a fully centralized assessment of APIs used for DMF registration.

RDC 359/2020: This guideline includes formats used for DIFA (DMF), and CADIFA applies to active pharmaceutical ingredients (API) utilized in producing innovative, innovator, generic, and comparable drug products. Hence, the new and current DMF will be assessed using RDC 359/2020 rule and regulation until further notice. (3)

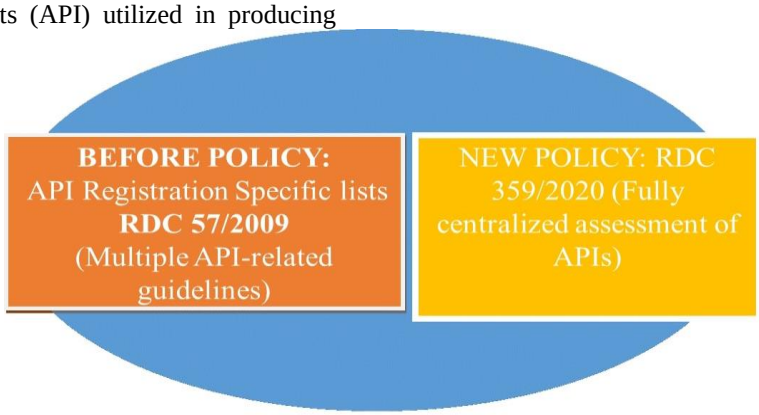

Figure 1. Before and New Policy of RDC (Resolution of the Collegiate Board of Directors)

New Definitions

DIFA - Dossiê de Insumo Farmacêutico Ativo

DIFA is an API dossier that contains drug master files and administrative documents. (5)

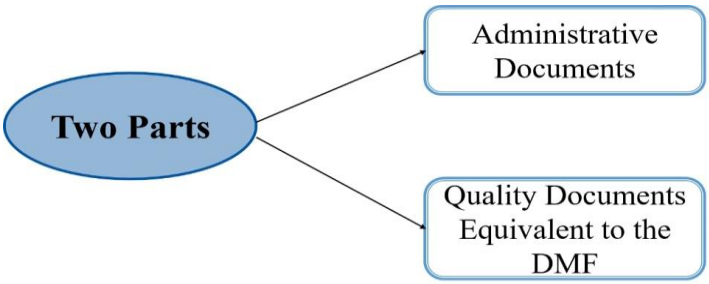

Figure 2. Parts of DIFA

DIFA HOLDER: The Company that has entire knowledge regarding the API manufacturing process, as they have in detail information related to the vital starting material and complete control over the API manufacturing process. (3)

CADIFA (Letter of Suitability of the Active Pharmaceutical Ingredient dossier): Administrative body attesting to the DIFA's compliance with Anvisa's regulations. ANVISA sent a letter after DIFA clearance. The DIFA holder must seek a CADIFA application. (3)

1.3 Introduction to Europe

European medical agency (EMA) & European Drug Master File (EDMF) are the regulatory bodies for the ASMF and CEP filing, respectively, in Europe. European Drug master file was established in 1989-1991. It was revised in 2003 and became an Active Substance Master File (ASMF) after implementing a CTD in Europe. The EDMF's primary goal is to assist a regulatory requirement of a drug product to verify its safety, quality, and efficacy, which further aids in the award of a Marketing Authorization. (4)

There are two types of DMF filing:

1. Active substance master file (ASMF)

2. Certificate of suitability to the monograph of the European (CEP)

ASMF and CEP

For a single active substance, the ASMF holder may have ASMF and CEP (Table No. 1) issued by the European Directorate for the Quality of Medicines and HealthCare (EDQM). It is unacceptable if the holder of a marketing authorization refers to both an ASMF and a CEP for a single active substance of Marketing Authorization Application (MAA) / Marketing Authorization Variation (MAV). A Marketing Authorization Application is a request for permission to commercialize a medication or treatment in the European market if the CEP provides sufficient information. (4)

Table 1. Comparison of CEP and ASMF

Certificate of Suitability (CEP) (4)	**Active Substance Master File (ASMF)** (5)
Only file for an existing active substance listed in an EU member state's pharmacopeia.	Filing for the existing active substance included or not included in the European pharmacopeia of an EU

	member state.
Not required individual filing in 27 member states.	Required individual filing in 27 member states.
The monograph's suitability for the control of the chemical purity of the drug substance and the herbal product is assessed.	The ASMF procedure cannot be used for the biologically active substance.
The EDQM is a regulatory authority to conduct the CEP	The EMA is the regulatory authority to conduct the ASMF.
The Digital Corpus of the European Parliament (DCEP) within EDQM is responsible for reviewing CEP.	Various working bodies within EMA are responsible for reviewing ASMF.
CEP submissions are to be made electronically. eCTD, NeeS, and PDF of modules 1 to 3 (each single PDF file) are bookmarked according to relevant subsections in each.	ASMF is to be submitted in separate two parts 1. Applicants part 2. Restricted part

1.4 Drug Master File (South Africa):

The South African Health Products Regulatory Authority (SAHPRA) is in charge of regulating the health products used in the country. SAHPRA assumed the responsibilities of the Directorate of "Radiation and Control of the Medicines Control Council", which was formerly situated under the National Department of Health. In South Africa, DMF is known as Active Pharmaceutical Ingredient Master File (APIMF). SAHPRA was established as an independent body that reports to the National Minister of Health through its Board of Directors. SAHPRA has decided to harmonize specific pharmaceutical policies and procedures; and the medicines agency. (6)

1.5 Common Technical Document (CTD)

Common Technical Document (CTD) is fixed of necessities for a Medicines Registration Application Dossier with a purpose to be utilized in Europe, Japan, the United States, and different Countries. CTD was created to standardize the presentation of technical data in human pharmaceutical product registration applications. (7-10)

The CTD dossier is organized into five major sections. Figure 3 represents the five different modules of the CTD.

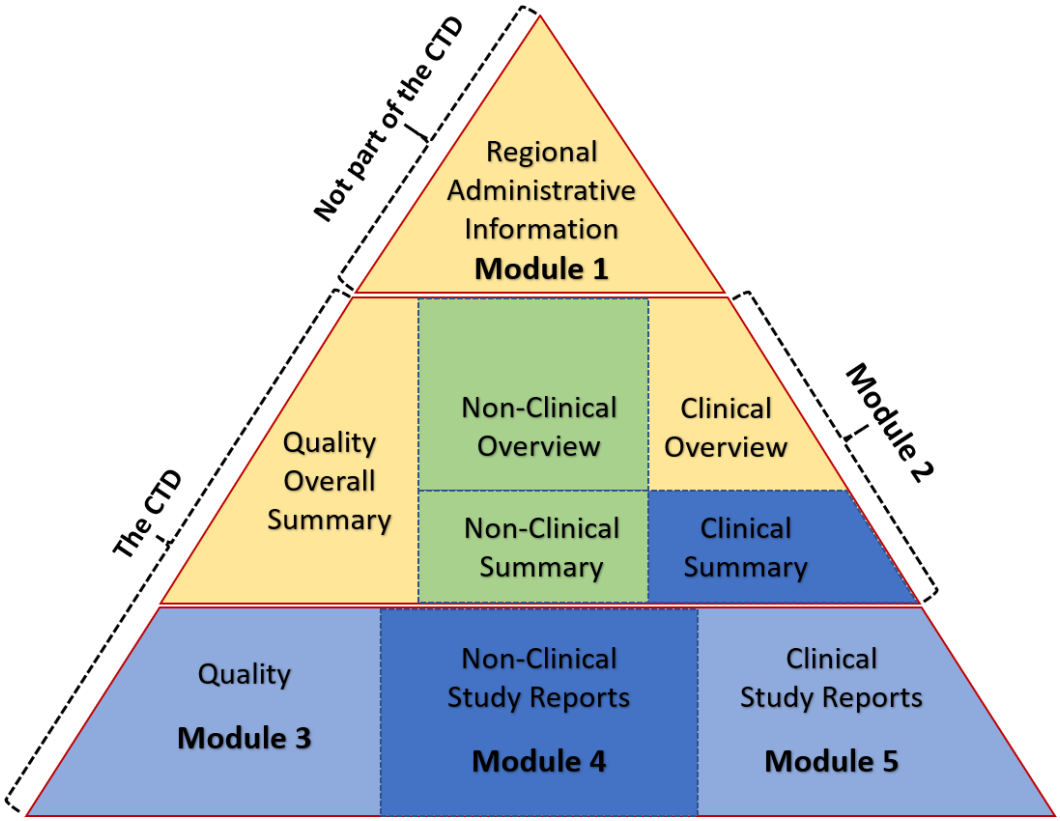

Figure 3. CTD Triangle

The Drug Master File comprises Modules 1, 2, and 3. Figure 4 represents the modules of DMF.

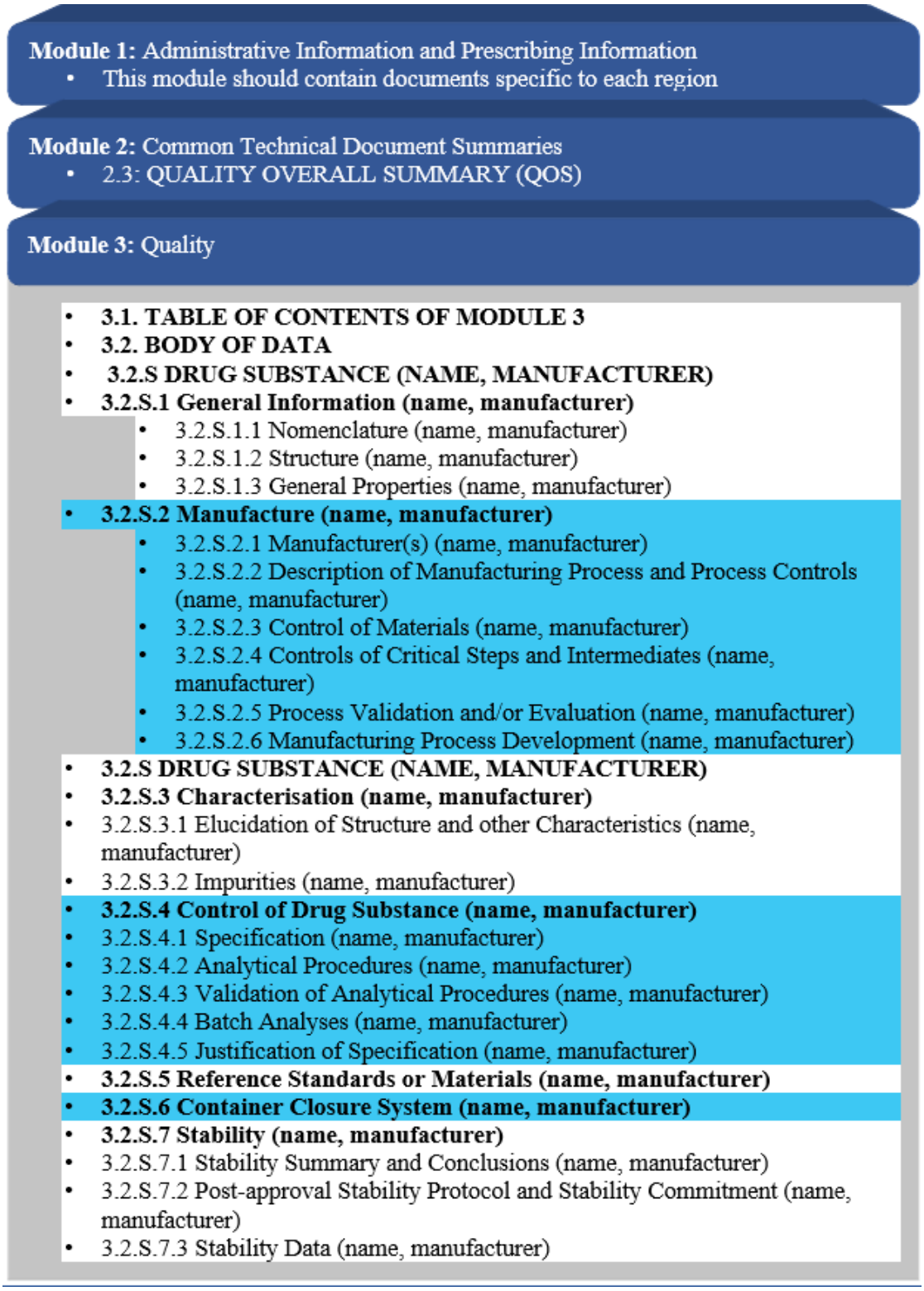

Figure 4. Module 1, Module 2, and Module 3 of Organization of CTD

2. Comparison of Regulatory Requirements

2.1 Comparison of Regulatory Requirements of DMF for Brazil, Europe & South Africa

Table 2 represents the comparison of regulatory requirements of Brazil, Europe, and South Africa and Europe provides the comparison for CEP and ASMF filling as well.

Table 2. Difference in Regulatory Requirements of Module 1 for DMF

CONTENT	BRAZIL	EUROPE		SOUTH AFRICA
		CEP	ASMF	
Flags				
Authority (3-6,8)	ANVISA (National Health Surveillance Agency)	EDQM (European Directorate for the Quality of Medicines & Health Care)	EMA (European Medicines Agency)	SAHPRA (South Africa Health Products Regulatory Authority)
CTD- Modules	Three Modules are involved: Module 1, Module 2, and Module 3	Three Modules are involved: Module 1, Module 2, and Module 3	Three Modules are involved: Module 1, Module 2, and Module 3	Three Modules are involved: Module 1, Module 2, and Module 3
Filing (eCTD/CTD)	CTD	eCTD	eCTD	CTD
Review time	2-3 months for initial queries. Depending on the questions asked, it could take up to a year to get approval.	6 Months for Initial queries	6 Months for Initial queries	NA
Fee	No fees	5000 Euro	No fees	No fees
Agent requirements	NA	NA	NA	NA
Language	Portuguese, English	English	English	English
Pharmacopoeia	Not mandatory European Pharmacopoeia (EP) / United State Pharmacopoeia (USP) based on applicant's request	Mandatory European Pharmacopoeia	Not mandatory European Pharmacopoeia (EP) / USP located on applicant's request	Not mandatory European Pharmacopoeia (EP) / United States Pharmacopoeia (USP) located at applicant's request
Module 1	Letter of Authorization if required Cover letters Query letters GMP certificate Application forms – customer-specific	Cover Letter Application Form Expert CV	Cover Letter Application Form Letter of Authorization Expert CV	Submission letter Information about the experts Letter of Access
Validity	No validity	After Approval, Renewal should be done after 5 Years	It is clubbed with a Formulation dossier and renewal at five years	It is Combined with a Formulation dossier and renewal at five years

2.2 Comparison of Contents in DMF – 3.2.S – Drug Substance (ICH-CTD)

Table 3 represents the comparison of regulatory requirements of Brazil, Europe, and South Africa and CEP and ASMF filling in Europe as well. [7]

Table 3. Difference in Regulatory Requirements of Module 3 for DMF

Content		Brazil	Europe (CEP/ASMF)	South Africa
Drug Substance (ICH-CTD)				
3.2.S.1 General information	3.2.S.1.1 Nomenclature	Brazilian Common Denomination (DCB) or INN (International Nonproprietary Name) (INN). API name Chemical Name Other names include the United States Adopted Name (USAN) and the British Approved Name (BAN)Chemical Abstracts Service registry (CAS) number; Product Code	API name Chemical Name Other names include the United States Adopted Name (USAN) and the British Approved Name (BAN) Chemical Abstracts Service registry (CAS) number Product Code	API name Chemical Name Other names include the United States Adopted Name (USAN) and the British Approved Name (BAN) Chemical Abstracts Service registry (CAS) number Product Code
	3.2.S.1.2 Structure	Structural formula Molecular formula Molecular weight (11)		
	3.2.S.1.3 General properties	Description (Appearance) (9) Solubility Solubility at different pH buffer pH pKa Log P Optical rotation Melting range Hygroscopicity Polymorphism Isomerism Therapeutic category		
3.2.S.2 Manufacturer	3.2.S.2.1 Manufacturer(s)	Agent details are not required.		
	3.2.S.2.2 Description of Manufacturing Process and Process Controls	Batch sizes related to the final API %yield Route of synthesis Process flow diagram Description of the manufacturing procedure Recovery of solvents Recovery material Reprocessing steps Blending batches, if applicable		
	3.2.S.2.3 Control of Materials	• Key Starting Materials (KSM) justification for starting material selection. List of materials used in manufacturing process based on starting materials such as: Name and address of the vendor Route of synthesis of starting material Impurity profile of starting material Analysis of starting material specification, method of analysis, and certificate Raw material specifications and test procedures, as well as certificates of analysis		
	3.2.S.2.4 Controls of Critical Steps and Intermediates	Critical process parameters In-process specification and method analysis Intermediate specification, method of analysis and COAs		
	3.2.S.2.5 Process validation	Detailed Process validation summary including (% Yield) Quality data of intermediate and API		
	3.2.S.2.6 Manufacturing process	Brief Manufacturing Process development history		

	development	
3.2.S.3 Characterization	3.2.S.3.1 Elucidation of Structure and other Characteristics	Mass spectrum 1H NMR spectrum 13C NMR spectrum IR spectrum Elemental analysis (CHNS) XRD analysis UV analysis
	3.2.S.3.2 Impurities	Organic impurities/ Related substances Residual solvents Inorganic impurities Elemental impurities Genotoxic impurities (if absent justification)
3.2.S.4 Control of Drug Substance	3.2.S.4.1 Specification	Appearance Assay Solubility Melting point Identification Impurities Total Impurities Loss on Drying Residual
	3.2.S.4.2 Analytical Procedures	Standard Test Procedure: Appearance Assay Solubility Melting point Identification Loss on Drying Related solvent General Testing Procedure: Assay Loss on Drying Residual Solvent
	3.2.S.4.3 Validation of analytical procedures	Analytical method validation reports for the determination of: Organic impurities Assay Residual solvents
	3.2.S.4.4 Batch analysis	Certificate of Analysis (CoAs) of at least 3 batches
	3.2.S.4.5 Justification of specification	Justification of specification in 3.2.S.4.1
3.2.S.5 Reference Standards	-	Characterization data of Working, Comparison (IR Overlay) of In-house standard with Compendial standards Validation data
3.2.S.6 Container Closure System	-	Primary packing material and secondary packing material Storage conditions Packing material supplier CoA and in-house test reports
3.2.S.7 Stability	3.2.S.7.1 Stability summary and conclusions	Stability studies summary Stability conditions Packaging description for stability Stability specifications Stability conclusion

	3.2.S.7.2 Post-approval stability protocol and stability commitment	Stability study specification Stability study protocol		
	3.2.S.7.3 Stability Data	Zone IVb (30ºC ± 2 ºC / 75% RH ± 5% RH) stability data. A microbiological test must be performed regularly, and its absence must be justified. Forced degradation studies HPLC analytical method validation report for API-related substances subjected to forced degradation Accelerated Stability Study Data Long term Stability Study Data	Zone I (21ºC ± 2 ºC/45%RH±5 % RH) Forced degradation studies Analytical method validation report for forced degradation API related substances by HPLC Accelerated Stability Study Data Long term Stability Study Data	Zone II (25ºC ± 2 ºC/60%RH±5% RH) Forced degradation studies Analytical method validation report for forced degradation of API related substances by HPLC Accelerated Stability Study Data Long term Stability study Data

3. Filing procedures

3.1 Filing Procedure of DIFA for Brazil

The filing procedure of DIFA for Brazil is represented in Figures 5and 6.

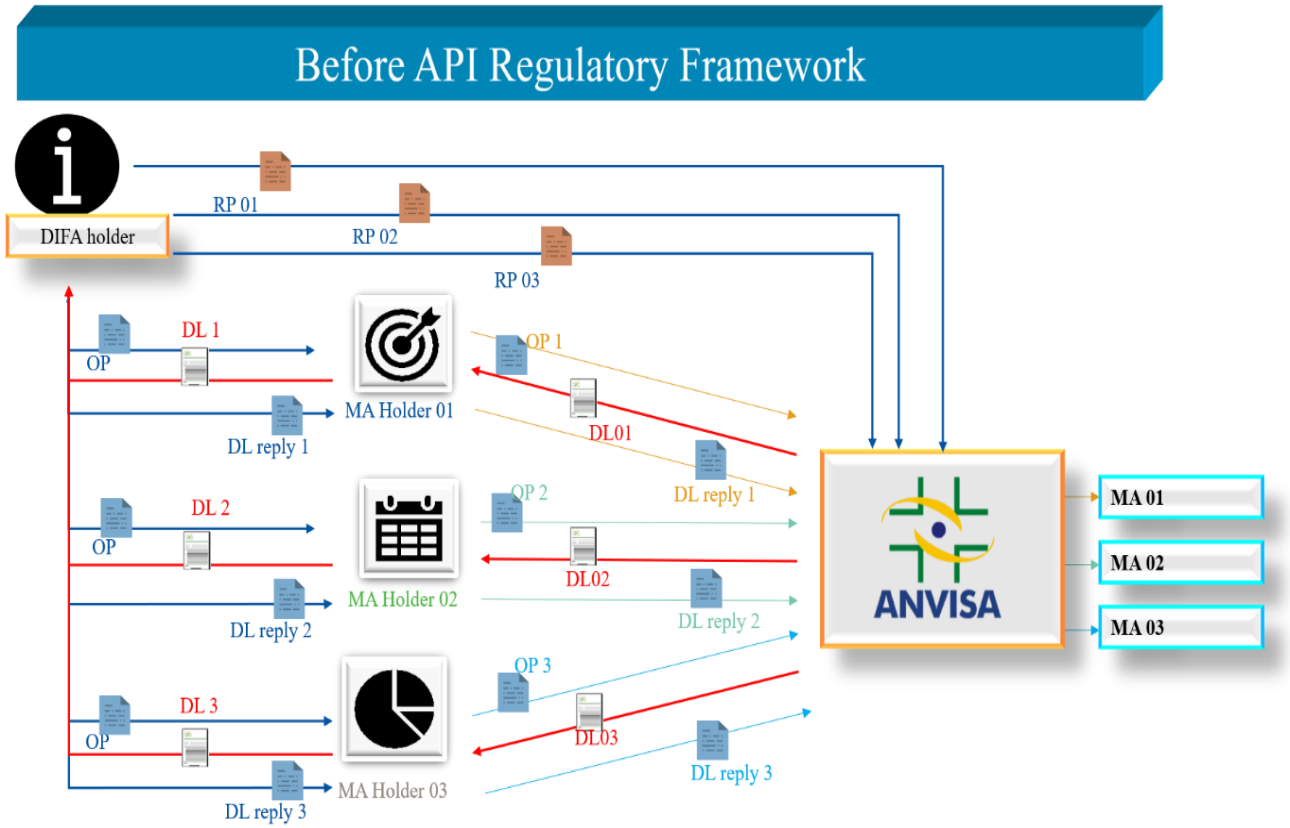

Figure 5. Before API Regulatory Framework for Brazil

The following flow chart represents the flow of the filing process before API regulatory framework.

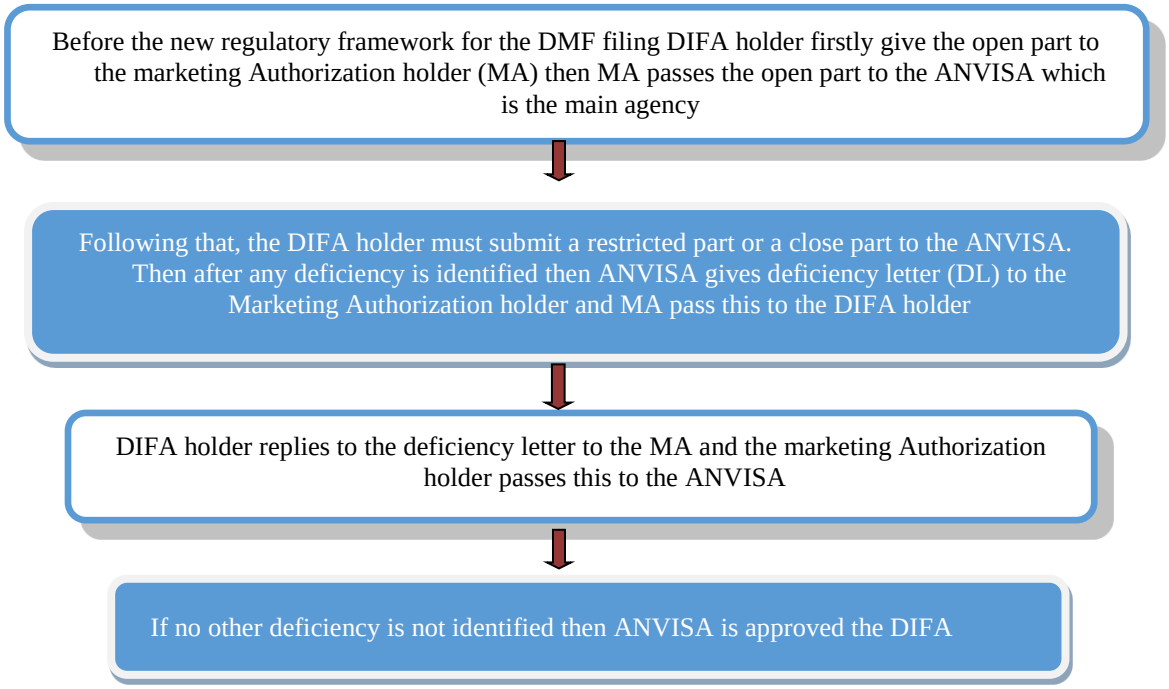

Figure 6. Filing process before API regulatory framework

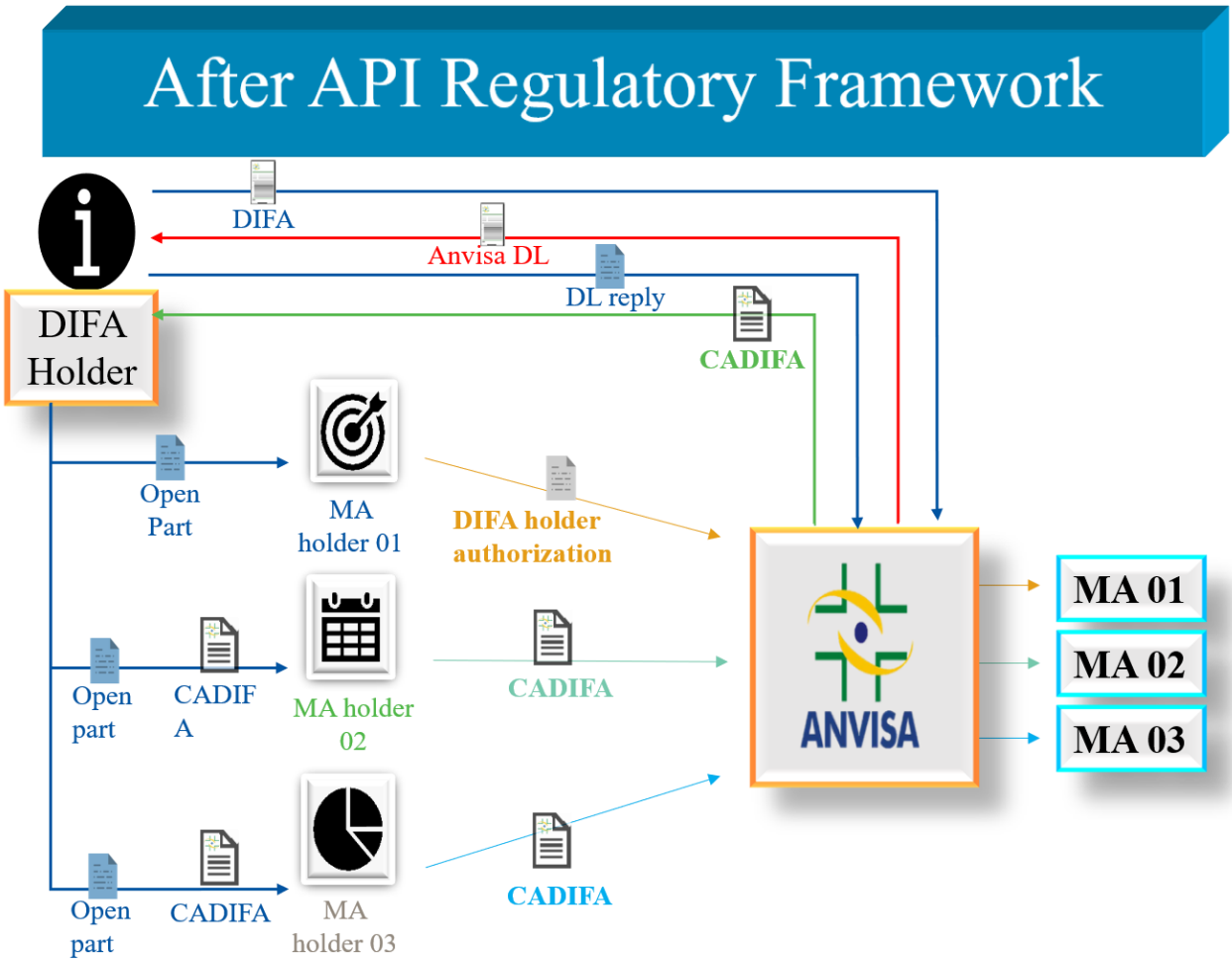

Figure 7. After API Regulatory Framework for Brazil

The following flow chart represents the flow of the filing process for the new API regulatory framework.

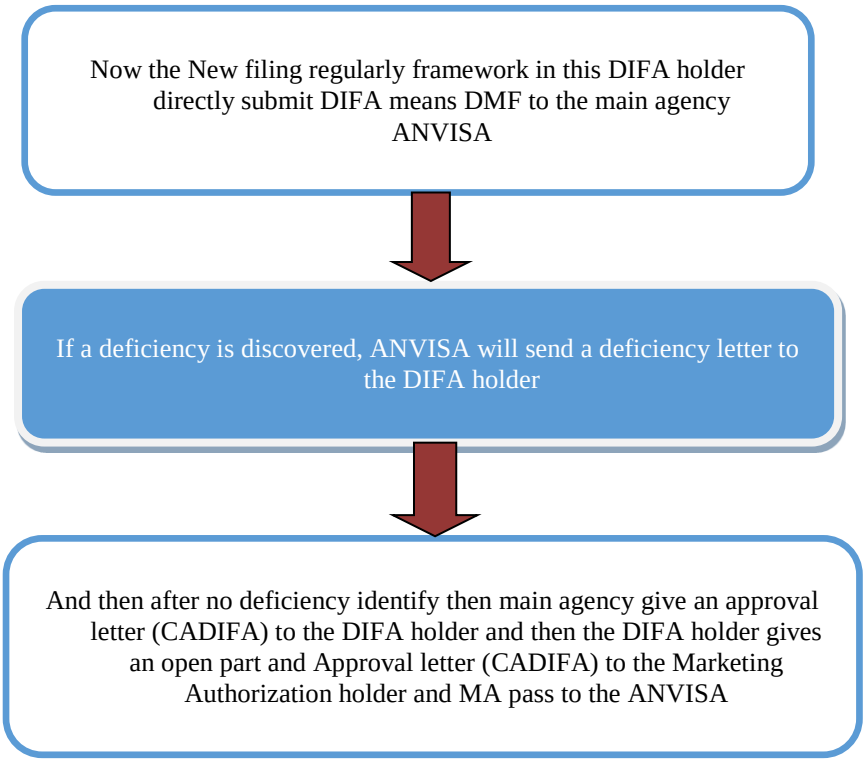

Figure 8. Filing process for the new API regulatory framework

3.2 Filing Procedure of Certificate of Suitability (CEP) for Europe

The filing procedure of CEP in Europe and the process is represented in figures 7 and 8:

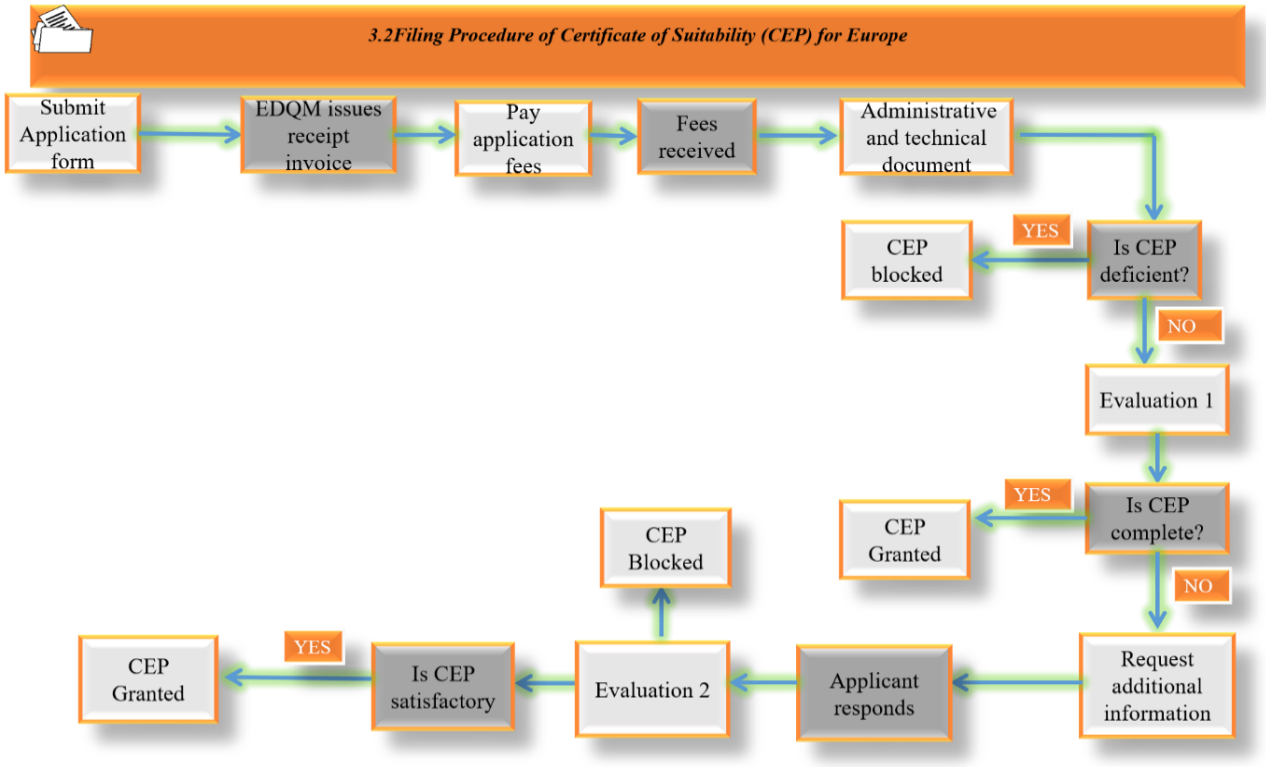

Figure 9. Filing Procedure of CEP for Europe

The following flow chart represents the flow of the filing process for CEP for Europe:

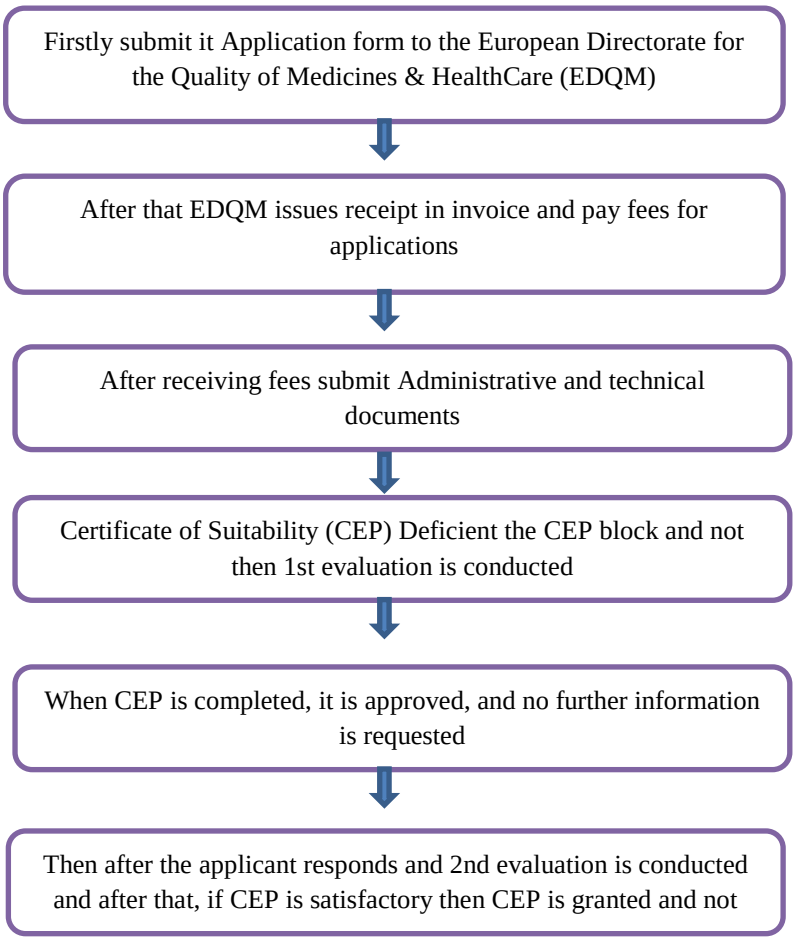

Figure 10. Filing process for CEP for Europe

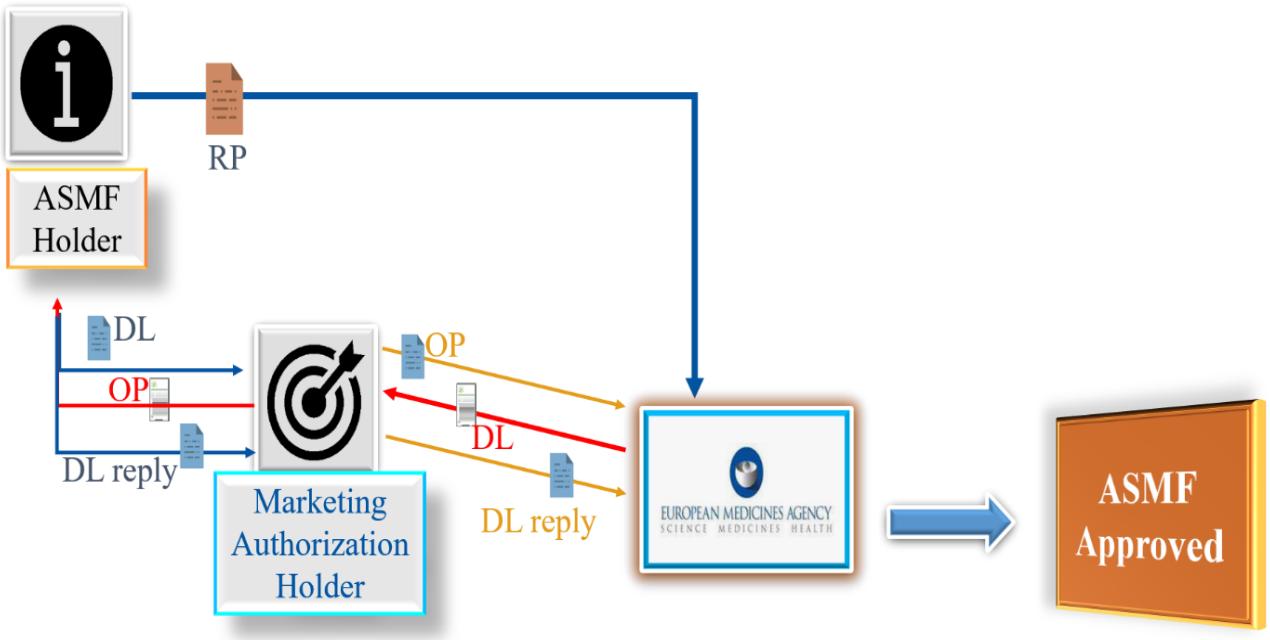

Figure 11. Filing Procedure of ASMF for Europe

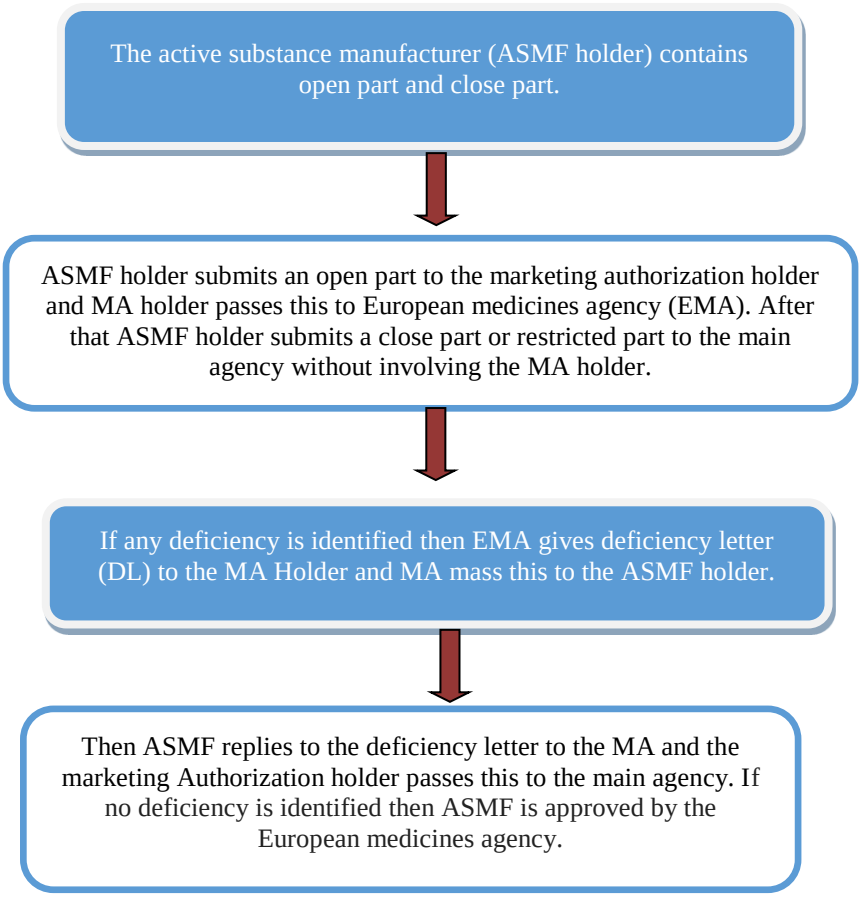

Figure 12. The flow of the filing process for ASMF for Europe.

3.3 Filing Procedure of Active Pharmaceutical Ingredient Master File (APIMF) for South Africa

The filing procedure of APIMF in South Africa and process is represented in figure 9.

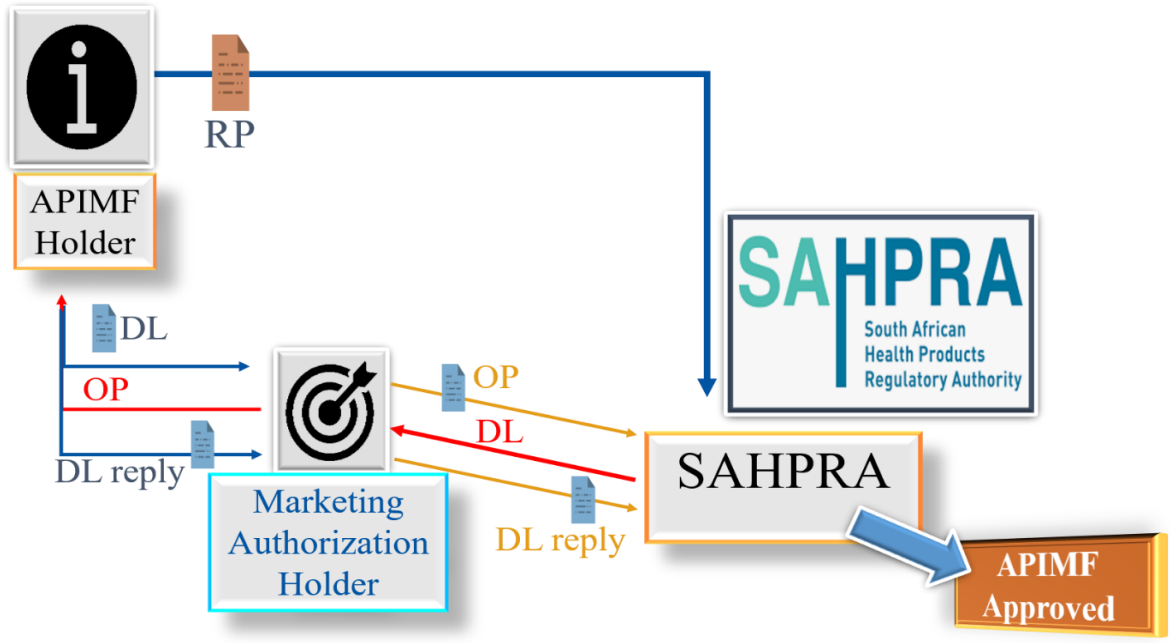

Figure 13. Filing Procedure of APIMF for South Africa

Filing Procedure of APIMF

The following flow chart represents the flow of the filing process for ASMF for Europe.

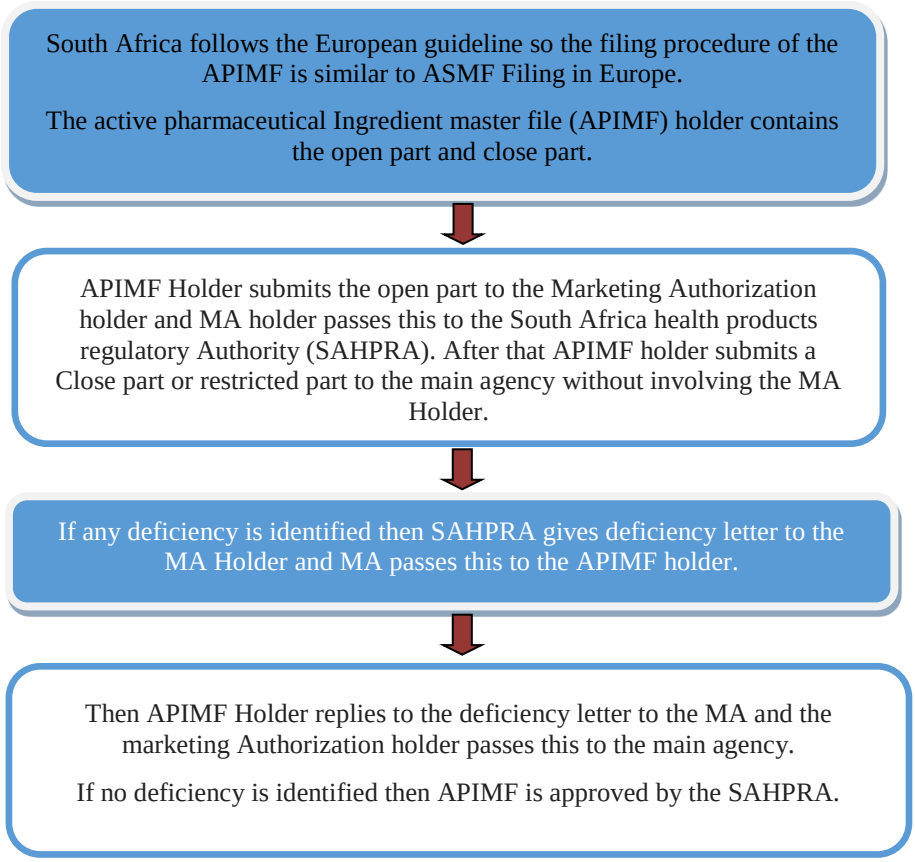

Figure 14. Flow of the filing process for ASMF for Europe

4. Conclusion

The quality of drug substances is essential in manufacturing robust and secure drug products. As a result, the Active pharmaceutical ingredient registration requirements must be detailed, and the approval of a Drug Master File must be finished cautiously and with discretion. The DMF is one of the most essential documents, as it is used to assist the application of a drug product. According to the comparison study, all regulatory areas follow ICH CTD Structure for the DMF filing process. In addition, each country is applying their internal regulatory guidance to fulfill these requirements (Such as stability condition differences in the Brazilian market).

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Conflict of Interest

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

Abbreviation

NSQ: Non Standard Quality

SFFC: Squirous/Falsely labeled/ falsified/ counterfiet

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