IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

STUDY ON DMF FILLING IN CONTEXT TO US, EUROPE, JAPAN AND ITS COMPARISON

Author name: [1]**Shaikh MD Shahzeb*, [2]Dr. K. S. Salunkhe**

[1]Designation: M pharm student (drug regulatory affairs)

Department: drug regulatory affairs

Name of organization: Sanjivani college of pharmaceutical education and research, kopargaon, Ahmednagar, Maharashtra, India

Abstract:

This is a collection of documents that provide full and accurate information on an active pharmaceutical ingredient (API) or a final medicinal dosage form in the pharmaceutical industry. It is now referred to as an active substance master file as a result of the European drug master file (ASMF). All prescription and over-the-counter medications in the United States are listed in a single database. The chemistry, manufacturing, stability, purity, and cGMP status of any human pharmaceutical product are all recorded in a drug master file (DMF) (DMF). In order to get an investigational new drug, new drug, or abbreviated new drug application, a DMF is required to meet regulatory standards and establish the medical product's quality, safety, and efficacy. To acquire market authorization, the drug master file must be structured and content differ from that of Europe (MA). To support regulatory requirements, the primary objective is to establish the product's quality, safety, and efficacy. A pharmaceutical company has created and presented this paper to the target market. There is no need to submit a DMF since there is no regulatory obligation. Confidential information concerning facilities, procedures, and products utilized in the production and processing of one or more human medicines is provided to the regulatory authority in this document. When two or more companies collaborate on the development or production of a drug product, a DMF is filed. Companies may safeguard their intellectual property by registering DMFs while still

meeting regulatory disclosure requirements for processing information A drug master file was compiled in a variety of ways across the US, Europe, and Japan, according to the findings. Drug master files administered by the Food and Drug Administration (USA), Japan's PMDA, and the European Medicines Agency (EMA) are also included (EMA). In order to submit a drug master file in the US, Japan, and Europe, you need this information. As a result of this research, you will have a better understanding of how to fill out a drug master file in the nations stated above, as well as what the differences are between the countries. The DMF primarily supports regulatory requirements pertaining to the proof of quality, safety, and effectiveness in order to help secure a pharmaceutical product's marketing authorization. To keep up with the latest regulatory submissions, this research examined new updates and revisions to the drug master file according to the eCTD or electronic format utilized by most regulated nations as of 2016.

Key words: drug master file, active substance master file, master file, eCTD, marketing authorization, API, USFDA, EMA, PMDA

US drug master file:

1.1) Introduction:

One or more human pharmaceuticals, as specified in 21 CFR 314.420, may contain sensitive and specific information regarding a company's production and processing techniques and materials. (3)

There are a variety of data sources that may be included in DMFs, including toxicological data and risk evaluation and mitigation strategies (REMS).

Instead of exposing private information, DMF holders may let one or more applicants or sponsors to utilize the DMF information for their own applications or sponsorships.

DMFs are not required to be submitted by law or regulation and are only filed at the request of their owners. For non-proprietary materials, they are seldom utilized. FDA does not normally conduct its own evaluation or approval of DMF applications. DMFs are rarely investigated by FDA purely for their technical substance when evaluating applications that refer to them.

However, the DMF is not a replacement for a new drug application (NDA), an abbreviated new drug application (ANDA), or an investigational drug application (IND). (2)

Points to Keep in Mind During the DMF Submission Process:

- DMF does not have regulatory status because it is not required to file by law.
- Types of DMFs are entered into the database Each form of DMF has its own database
- It has been notified by central drug registration (CDR).
- There is no reviewer assigned to you, and there is no deadline.
- DMF reviewed Only when a DMF is referred by an application or another DMF.
- FDA will not issue a reminder if a company misses their yearly update due date. (2)

Guideline for drug master file in US:

1. According to the Food, Drug, and Cosmetic Act, 21 CFR 314.420 supports new drug applications, abbreviated new drug applications (ANDAs), and investigational new drug applications (INDs) (FD&C Act).
2. Files used to support the submission of biologics license applications (BLAs) in accordance with 21 CFR 601.51(a) (PHS Act) of the Public Health Service Act.

DMF's Function:

- To demonstrate an understanding of documentation for the registration and approval of pharmaceutical products.
- This document explains in detail how a medicine is identified, purified, strong, and of high quality in the CMC parts of the submission.
- To ensure the security of proprietary and private information. (4)

Table No 1.1: Application and DMF: What is the difference?

Application	Drug master file
It falls under regulatory pathway must be filed by applicant its mandatory.	It Does not falls under regulatory pathway it is not mandatory to file a DMF.
In application each section and supplement has common database.	In DMF there are different types according to their type has a database.
Submission of Application to the respective review division.	submission of DMF to the central drug registration.
Each submission is assigned to a reviewer and given a due date.	There is no reviewer assignment and no deadline date.
If the annual update due date is missed, FDA sends a reminder.	If the yearly update due date is missed, the FDA will not send a reminder.
The review procedure is considerably different from the DMF.	DMFs are only reviewed when they are referred to in an Application or another DMF.

Table no 1.2: Types of Drug master file:

Section 314.420 of the US-FDA outlines four different types of drug master files. (5)

Type of DMF	Information contain in the DMF
Type 2	Drug substance, drug substance intermediate, and materials used in their preparation, or drug product.
Type 3	Packaging material.
Type 4	Excipient, colorant, flavor, essence, or material used in their preparation.
Type 5	FDA-accepted reference information.

However, since 2000, the numbering of the other DMF kinds has remained constant. When it comes to terminology for the various types of master files required for goods covered by the PHS Act and the FD&C Act, the FDA has chosen a similar approach. (5)

Type 1: Site, facilities, operational processes, and employees in the manufacturing industry.

An FDA on-site inspection of a manufacturer's facility can be aided by a DMF Type I if the inspector is from outside the United States. The DMF document should contain information about the production facility, its equipment, and its operating design. Type I DMFs aren't required in most cases unless in cases when the patient isn't registered and frequently evaluated.

The description of the property should include information such as the number of acres, the position of the site in relation to the closest city, and a map showing its exact location. An aerial shot and a site diagram might be helpful. A depiction of the primary manufacturing and processing areas helps explain the operating architecture. Large pieces of equipment need to have their capabilities, use, and placement specified. Unless the equipment is new or unusual, it is usually not necessary to know the brand and model. Also helpful are diagrams that show key components of a company's structure, such as manufacturing and quality control jobs. (6)

Type 2: a drug substance, a drug substance intermediary, and the ingredients needed to make it, or a drug product.

In general, only one drug intermediate, component, drug product, or material type should be utilised in the production of a Type II DMF. (6) Intermediates, finished drugs, and the raw materials used to make them For example, describe in detail how a drug intermediate or chemical is made and controlled. IND, NDA, ANDA, and export files should almost always include the final dosage forms. If a DMF did not involve this information, an IND, NDA, ANDA, or export application must include it. Drug Master File (DMF) for a drug product's Type II. (6)

Type 3: Packaging material.

Packing materials need to be classified according to their intended use, their components and composition, and their release regulatory systems. It is essential to include the names and acceptance requirements of the component suppliers or fabricators utilised in the preparation of the packaging material. Documentation confirming the packaging's suitability is also required, as per the Packaging Documentation Submission Guidelines for Human Drugs and Biologics. It would be possible to get toxicological data on these substances. contained in this sort of DMF if it can't be traced in another document through a cross reference. (6)

Type 4: Material or ingredient that was used in the manufacture of the product.

Manufacturing processes, release standards, and testing methods should all be used to identify and differentiate each additive. This kind of DMF would include toxicological information on these substances if it was previously unavailable through a cross-reference to another record.Various food additives (21 CFR Parts 70–82), colorant additives (21 CFR Parts 170–173 and 174–178), indirect food additives (21 CFR Parts 174–178) and food substances (21 CFR Parts 181–186) are frequently used in release testing, standards, and safety for food. A Type IV DMF may benefit from the advice given for preparing a Type II DMF. (6)

Type 5: FDA-accepted reference information.

When it comes to information that is repetitive, redundant, or may be found in another DMFS, the FDA advises against using Type V DMFs. To submit information and supporting data not covered by Types I–IV, a holder must send a letter of intent to the Drug Master File Staff. A representative from the FDA will contact you to go over your submission strategy as a result. A single Data Management Framework (DMF) should contain only one type of information and all of its supporting data. (6)

1.2 Submission of DMF:

Each submission must include a transmittal letter as well as sufficient administrative information. It must be written entirely in English. If it includes material in another language, it must be accompanied by an accurate certified English translation. In the DMF, each page must be correctly dated and numbered, and the table of contents must be updated. The specific contain in transmittal letters and administrative information are given in the table no Table 2.1: Information must be containing in transmittal letters. (7)

Sr.no	Content	Details
1.	Original submission	• Name and address of each sponsor, Applicant or holder. • Sign of the holder or authorized representative. • Typewritten name and title of the signer.
2.	Amendments	• The DMF number, type of DMF and the subject of Amendment. • Short description of the purpose of the submission like update revised formula or process. • Sign of the holder or authorized representative. • Typewritten name and tittle of signer.

Table no 2.2:data must be containing in administrative information. (7)

Sr.no	Content	Details
1.	Original submission	• Name and addresses and specific responsibilities of DMF holder, corporate head quarter, manufacturing or processing facility, content of FDA correspondence and agent. • Statement commitment: A signed statement by the holder certifying that the DMF holder will comply with the statement made in it.
2.	Amendments	• Name of DMF holder, DMF number, name and addresses of correspondence affected section or page number of the DMF. • The name and address of each person whose IND, NDA, ANDA, DMF or other export application relies on the subject of the amendment for support.

1.2) General information or recommendations and new updates:

1) **Environmental assessment:**

There should be a strong guarantee that the facilities of Type II, Type III, and Type IV DMFS would be operated in conformity with all relevant regulations. If there is According to 21 CFR Part 25, a complete environmental assessment is necessary. (7)

2) **Stability:**

Under the "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics," stability study design, results, interpretation, and other relevant information should be included. (7)

3) **Format, assembly and delivery:**

All DMF submissions must include both an original and a two copies. For the rest of the life of their FDA submissions, holders of Drug Master Files and their agents/representatives are required to maintain a complete reference copy. It is imperative that all of the originals and duplicates be correctly assembled, collated, and packaged in separate covers. A DMF volume should have a maximum thickness of 2 inches. A multi-volume submission should be given a unique number for each book. An example of this would be the numbering of a three-volume submission as follows: Volumes 1 of 3, 2, and 3 of 3. (7)

The most common paper size in the United States is 8 1/2 by 11 inches. Ten to twelve inches is an ideal length for a paper. For a floor layout, synthesis flowchart, batch formula, or production instructions, a sheet of paper larger than ordinary paper size may be necessary. When the set is stored away in a cabinet or other storage area, fold and mount the pages such that they may be accessed without detaching the jacket and refolded without causing harm. (7)

4) Format and new update for ECTD submission:

The deadline for submitting eCTD Drug Master Files (DMFs) has been extended to May 5, 2018, by the United States Food and Drug Administration (USFDA). Applicants have less than two months left must ask themselves the most critical question: What are the DMF Type requirements, and how should the data be prepared, verified, and distributed to ensure successful electronic submissions? Let's take a look at the FDA's most recent DMF modifications before diving into those questions. Any DMFs submitted after the May 5, 2018, recommended date would be rejected by the FDA, according to the legislation. (8)

e-CTD submissions do not need re-filing of previously filed DMFs with the FDA in paper format. On the other hand, any new entries submitted after May 5, 2018, must be in the e-CTD format. It is possible for DMF holders to preserve their original DMF numbers, with a few

minor alterations. Suppose the previous DMF number was 5678, and the DMF holder now has to pad to the left with two zeros, as seen in this example. As a result, 5678 becomes 005678 when converted from DMF to e-CTD format, but else stays the same. (8)

The ECTD application Submitting a DMF through the Electronic Submissions Gateway (ESG) is required under section 745A if the submission is less than 10 gigabytes in size and includes a DMF number (ESG). It is possible to send huge files through ESG, or to send physical media (e.g. CDs) with a cover letter and delivery costs pre-paid as mentioned below. DMFs commonly use the eCTD electronic format (electronic common technical document). (5)

5) Packaging information not necessary included in DMF

Packaging information is not required by the FDA in the DMF. Information on packaging components must be included in NDA applications (and even sponsors of an IND or BLA or ANDA). The maker of the aforementioned packaging component or material may make this information accessible to the applicant or include it in the application. (8)

An authorization letter from the manufacturer referencing a Type III DMF may be included to the application if the manufacturer desires to keep some proprietary information from the applicant or sponsor, and all such information can be included in the application accompanied by the DMF. There is no need to submit a DMF in e-CTD format if it is already on file in paper form with the FDA. There will be a switch to e-CTD submissions on May 5, 2018, which will make paper submissions obsolete. (8)

6) Original Submissions:

Before submitting an original DMF in eCTD format, DMF holders must get a pre-assigned number. http://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number for CDER submissions. (5)

Send an encrypted email to: cberrims@fda.hhs.gov to obtain an application number for CBER submissions, as well as sponsor/applicant name and address, point of contact name, and product name.

All first submissions must include complete administrative and technical information in the applicable eCTD modules. Both first and subsequent DM submissions include section titles that allude to change and sponsor/applicant even if these terms aren't included in module names. (5)

7) Other recommendation:

A) English translation:

Non-English parts of the NDA or ANDA must be translated into English precisely and fully (314.50(g)(2), 314.94(a) (11)). The same may be said with DMFs. It is not necessary to obtain a certified translation.

B) Public availability

21 CFR part 20 and any related FDA disclosure rules, such as sections 314.420(e), 314.430, and 601.51, control the availability of DMF information to the general public. Information can be exchanged among DMF holders and approved parties in whatever preferred manner.

C) If holder is not the manufacturer

The FDA assumes that anybody possessing a DMF is a producer of the substance for which the DMF was granted. Holders of DMFs must bear full responsibility for any items covered by the DMF even if they are not the manufacturers. (5)

1.3) CTD/ECTD Format and content Drug master file:

(Table no 1.5 CTD open part) (7)

Part	Information containing in module
2.0	Common technical document summaries
2.3.S	Quality overall summary
2.3.S.1	General information
2.3.S.2	manufacture
2.3.S.3	characterization
2.3.S.4	Control of the drug substance
2.3.S.5	Reference standard
2.3.S.6	Container closure system
2.3.S.7	Stability
3.0	Quality (chemical and pharmaceutical information)
3.2.S	Drug substance
3.2.S.1	General Information
3.2.S.1.1	Nomenclature
3.2.S.1.2	structure
3.2.S.1.3	General properties
3.2.S.2	manufacture
3.2.S.2.1	manufacturer
3.2.S.2.2	Description of manufacturing process and process controls
3.2.S.2.2.1	Flow chart of manufacturing process
3.2.S.2.2.2	Synthetic route of manufacturing process
3.2.S.2.2.3	Manufacturing process details
3.2.S.2.3	Controls of raw materials
3.2.S.2.4	Controls of critical steps and intermediate
3.2.S.2.5	Process validation
3.2.S.2.6	Manufacturing process development
3.2.S.3	Characterization
3.2.S.3.1	Elucidation of structure
3.2.S.3.1.1	Elemental analysis
3.2.S.3.1.2	Infrared spectrum of drug substance
3.2.S.3.1.3	NMR Spectrum of the drug substance
3.2.S.3.1.4	Mass spectrum of the drug substance
3.2.S.3.1.5	UV spectrum of the drug substance
3.2.S.3.2	Impurities
3.2.S.3.2.1	Potential impurities

3.2.S.3.2.2	Analysis of working standard for determination of potential impurities
3.2.S.3.2.3	Validation of analytical methodology for the estimation potential impurities
3.2.S.3.2.4	Residual solvent impurities
3.2.S.3.2.5	Validation of analytical methodology for the estimation of residual solvent impurities
3.2.S.4	Control of drug substances
3.2.S.4.1	Specification
3.2.S.4.2	Analytical procedure
3.2.S.4.3	Validation of analytical procedure
3.2.S.4.4	Batch analysis
3.2.S.4.4.1	Certificates of analysis
3.2.S.5	Reference standards
3.2.S.6	Container and closure
3.2.S.4.6.1	Packaging details
3.2.S.4.6.2	Specification for packaging material
3.2.S.7	Stability
3.2.S.7.1	Stability summary and conclusion
3.2.S.7.2	Post Approval stability protocol and stability commitment
3.2.S.7.3	Stability data

(Close part)

3.2.S.2	Manufacturer
3.2.S.2.1	Manufacturer
3.2.S.2.2	Description of manufacturing process and process control
3.2.S.2.2.1	Flow chart of marketing process
3.2.S.2.2.2	Synthetic route of manufacturing process
3.2.S.2.2.3	Manufacturing process details
3.2.S.2.3	Control of raw materials
3.2.S.2.4	Controls of critical steps and intermediates
3.2.S.2.5	Process validation
3.2.S.2.6	Manufacturing process development
3.2.S.4.5	Justification of specification
3.2.S.5	Reference standards
3.2.S.6	Container and closure system
3.2.S.6.1	Packaging details
3.2.S.6.2	Specification for packaging materials

1.4) ECTD module content:

Module 1:

A) Cover letter (ectd section 1.2)

The kind of submission should be specified in the cover letter (e.g., original, agent appointment).

For the cover letter, it is essential that the DMF owner sign off on it, making a commitment to adhere to all of the DMF's obligations. (5)

b) Administrative information (ectd section 1.3)

DMF holder, agent, manufacturer, and debarment certificate should all be included in this section of administrative information.

1. DMF holder:

DMF holders are required to submit their name and address. As the DMF holder, only one firm should be named. Joint submissions will not be accepted.

2. Agent:

Holders of DMFs are required to provide contact information, including name, phone number, fax

number, email address, and any specific responsibilities (if different from the contact person).

An agent familiar with FDA regulations, standards, and processes is highly recommended by the FDA for international DMF holders to enhance communication. The contents of their DMFs (such as CMC information) are the responsibility of the DMF holders, not their agents. (5)

Agents can submit on behalf of DMF holders to the DMF. Except for the following, they may sign DMF contributions:

- ✓ Agent appointment letters.
- ✓ Statements of commitment.
- ✓ Name changes.
- ✓ Holder transfers.
- ✓ New holder acceptance letters.
- ✓ DMF closure requests.

3. Manufacturer:

The manufacturer's name, location, contact person's name, phone and fax numbers, and email address must be included in the DMF.

4. Debarment certification:

As established in Section 306(k)(1) of the FD&C Act, "Persons engaged in whatever capacity," an application's "Subjects" are defined. In compliance with eCTD section 1.3.3, DMF holders may submit their own debarment certifications. (5)

A) References (section 1.4)

I. Letter of authorization

A letter from the DMF holder authorizing them to include all or part of the DMF's content by reference is required to support an application, supplement, or another DMF, or a change to any of these papers. The FDA's LOA permits an examination of pertinent sections of the DMF as well.

DMFs are not taken into consideration by the FDA unless a LOA is provided by the DMF holder for a particular application or another portion of the DMF (314.420(d)). It is possible to submit a LOA as an addendum to an initial application or to a new application altogether. (5)

An authorized party (i.e., the company or individual submitting a DMF) can also reference content in an application or another DMF thanks to the LOA, as well (eCTD section 1.4.1). Letter of authority (LOA) is necessary, regardless of whether the DMF holder and authorized party are the same company. (5)

A copy of the LOA should be provided by the DMF holder to an authorized party. The authorized party's application or DMF must contain a copy of the LOA (314.50(a)(1)) (eCTD section 1.4.2). A LOA does not allow access to a DMF to an authorized user. (5)

The following information should be included in the authorization letter

1.The date.
2. Name of DMF holder.
3. DMF number.
4. Name of person(s) authorized to incorporate information in the DMF by reference.
5. Specific product(s) covered by the DMF. 6. Submission date(s) of 5, above.
7. Section numbers and/or page numbers to be referenced.
8. Statement of commitment that the DMF is current and that the DMF holder will comply with the statements made in it.
9. Signature of authorizing official.
10. Typed name and title of official authorizing reference to the DMF. (1)
List of authorized individuals to be incorporated by reference.

This section of the eCTD clarifies who is permitted to incorporate any DMF element by reference going forward. When a new LOA or an authorised party is added or removed from the list, the list should be updated. The following information should be included in the list for each permitted par: (5)

- The LOA's expiration date.
- The LOA's specific products, materials, or procedures, including submittal
  Dates, eCTD section numbers, and page numbers are all included.
- An application number that refers to the DMF (optional).
- The authorized party's name.

B) Application status (Ectd section 1.5)

Disclose DMF using section 1.5.5

If the FDA cannot verify the validity of the DMF, the DMF may be closed at the request of the DMF's holder. A DMF may need to be updated in this scenario. The FDA will contact either its holder or agent. FDA may

terminate a DMF and notify the holder or agent if the holder or agent fails to submit an annual report on time.

A DMF holder must request administrative closure in order to close a DMF. All authorised parties must be notified of the closure in the request for closure (eCTD section 1.5).

C) Meetings (eCTD section 1.6).
D) Modules 2 through 5 do not cover the following information: (eCTD section 1.11).
E) Other correspondence (eCTD section 1.12)
F) Labeling (eCTD section 1.14)

For Type II and Type IV DMFs, the Labeling section of the application must include a copy of the shipping label.. (5)

G) Identifying and resolving potential threats (eCTD section 1.16).

Module 2:

In Module 2, you'll discover all 3 of the necessary modules (and 4 and 5, if applicable).

Module 3:

Manufacturers must follow current good manufacturing practices when developing DMFs for substances, intermediates, pharmaceuticals, and intermediates of finished goods (eCTD sections 3.2.S.2 or 3.2.P.3). (5)

Module 4: DMFs without nonclinical assessments are excluded from this criterion unless the impurity's CMC information is included in module 3 of a Type IV DMF or module 3 of a Type II DMF.

Module 5:

It is recommended that Module 5 only be used in clinical settings, such as a Type V DMF.

1.5) Drug master file containing information according to their Type:

Type 2 drug master file:

Each Type II DMF should concentrate on a specific drug component, intermediate, material type utilised in production, or drug product. Type II DMF also includes drug product intermediates. If a drug compound is made using a variety of methods, it must be submitted in several DMFs.

Good manufacturing practices (cGMPs) must be included in DMFs for drugs, drug intermediates, drugs, and intermediates for drugs (eCTD sections 3.2.S.2 or 3.2.P.3).

If an FDA evaluation of a material utilised in the manufacturing process of a drug substance or a drug substance intermediate is required, then a Type II DMF should contain CMC information (for example, specific artificial cell growth medium). (5)

Type 3 drug master file:

There should be a clear labelling of the package (bottle), as well as the material of construction (MOC) (e.g., high-density polyethylene). A variety of packaging materials can be utilised in a variety of ways to create container closures (e.g., a syringe barrel and a plunger).

Direct delivery of MOC component information, including safety data, to the authorised party is possible without filing a DMF.

This kind of data may include information on the container-closure system, materials of construction (MOC), release control mechanisms (RCM), and intended usage. It is possible to add the names of the MOC or component manufacturers and suppliers, as well as the requirements for approval. (5)

Type 4 drug master file:

Lactose and Microcrystalline Lactose are two different types of lactose. The excipients, which are mixtures of numerous chemicals, should be specified in eCTD section 3.2.S as examples of substances (such as flavourings).

DMFs should be utilised for excipients for which the USP551 NF or related laws does not provide access to CMC and safety information, or quality information. Among them are new excipients and colours, as well as aromas, essences, and materials used in their production. (5)

Type 5 drug master file:

REMS, sterile processing facilities, and toxicological studies for drug compounds are examples of Type V DMFs that can be submitted by DMF holders who want to provide information not covered by Types II–IV, but first they must email a letter of intent to the DMF staff at dmfquestion@hss.gov before they can submit a Type V DMF. A consultation with the DMF holder will be scheduled by the FDA soon to go through the details of the planned submission. (5)

1.6) DMF to be updated annually:

Annual updates are required for holders of DMFs as per the DMF Guidance. "Overdue Notification Letters" are also sent to DMF holders who've not updated their paperwork in the last three years. The FDA may cancel

a DMF holder's account if he or she does not respond to an ONL. (8)

1.7) Submissions Sent Subsequently:

The DMF must be notified of any modifications, additions, or deletions to the content in the DMF, including LOAs. A cover letter, as well as any new administrative or technical data, should be included with the following submissions. The expression of commitment should be included in DMF holder name updates and acceptance notices.

A) Cover letter:

It is necessary to report any changes to administrative information (such as a change in agent) in the form of an administrative amendment, as well as any changes to technical information (such as a change in the test procedure) in the form of a quality amendment, and any changes to risk evaluation and mitigation strategy information (such as an important move to the REMS). (5)

B) Administrative Amendments:

(Name changes, acquisitions, or transfers of ownership)

According to section 314.420(c) of the FDA's rules, name changes must be communicated in an administrative update to each DMF held by a DMF holder. As a result of a DMF holder being bought by or transferred to another entity, the company's name may be altered. Whether the prior DMF holder engaged an agent and the new DMF holder retains that agent or engages a new agent, the current DMF holder must send agent appointment letters. The original DMF holder must notify the DMF of the transfer, and the new DMF holder must notify the DMF of their acceptance of it. Declare your committed to respecting the DMF's terms and conditions by signing a declaration of commitment when notifying others of a name change or acceptance. (5)

(Changes to the DMF subject)

When the topic of the DMF changes, administrative updates are required (title). Due to changes in technical information, such as when a drug substance's grade has been revised, the DMF should be changed as well (for example, by changing its title). (5)

(Changes to the DMF type)

DMF type changes must be made through administrative updates. The DMF holder should file a quality revision if the type change necessitates changes to the DMF's technical information. (5)

C) Amendments of High Quality:

A quality amendment must be submitted for any changes to technical information.

D) Conversion of Existing DMFs to Comply with eCTD Format

A cover letter summarizing the content changes made as a result of the conversion should be included by DMF holders who wish to resubmit previous DMF submissions as eCTD submissions. There is no need to re-register your DMF number. Two zeros must be added to the front of any four-digit number (for example, 1234) in the eCTD's six-digit format, such as 001234.. (5)

1.8) Upcoming Drug master file form 3938:

For submissions of the Drug Master File (DMF), it provides a standardized electronic fillable form. Allow the FDA to automatically enter DMF data. Data from eCTD (electronic Common Technical Document) DMF submissions should be captured. All eCTD submissions of DMFs should include Form 3938.

The eCTD requirement does not apply to Type III DMF. ESG accepts both eCTD and non-eCTD submissions. Non-eCTD submissions can be made using the CDER NextGen Portal.

1. Date of Submission *(mm/dd/yyyy)*	2. DMF Number
12/20/2020	123456

3. DMF Subject *(Title)*
Madeupthricin

4. DMF Type *(Select one)* ☒ II ☐ III ☐ IV ☐ V

5. Holder Information

Holder Name	Holder DUNS Number
Magic Kingdom, Inc.	984123654

Holder Address

Address 1 *(Street address, P.O. box, etc.)*
1000 Fun Street

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City	State/Province/Region
Orlando	Florida

Country	ZIP or Postal Code
USA	32801

Holder Contact *(Name of person)*	Holder Contact Telephone Number *(Include country code, if applicable, and area code)*
Goofy Dawg	(111) 987-6543
Holder Contact Email Address	**Holder Contact FAX Number *(Include country code, if applicable, and area code)***
goofydaug@magic.net	(111) 987-5432

6. DMF Agent *(Recommended for DMFs submitted by non-U.S. companies)*

DMF Agent Name
ABC Company LLC

Agent Address

Address 1 *(Street address, P.O. box, etc.)*
2222 Epcot Way

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City	State/Province/Region
Laurel	Virginia

Country	ZIP or Postal Code
USA	22046

Agent Contact *(Name of person)*	Agent Contact Telephone Number *(Include country code, if applicable, and area code)*
Mr. John Smith	222-123-4567
Agent Contact Email Address	**Agent Contact FAX Number *(Include country code, if applicable, and area code)***
JSmith@abccompany.com	Not Available

Scenario 1

7. Submission Type *(May select more than one)*

- [x] Original (New)
- [ ] Administrative Amendment
- [ ] Annual Report
- [x] Letter of Authorization
- [ ] Withdrawal of Letter of Authorization
- [ ] Meeting
- [ ] Quality Amendment
- [ ] Response to Administrative Filing Issue
- [ ] Response to Deficiency, Complete Response, Information Request or Additional Comments Letter
- [ ] REMS - Risk Evaluation and Mitigation Strategy
- [ ] Other *(Specify)*:

Scenario 2

7. Submission Type *(May select more than one)*

- [ ] Original (New)
- [x] Administrative Amendment
- [ ] Annual Report
- [x] Letter of Authorization
- [ ] Withdrawal of Letter of Authorization
- [ ] Meeting
- [x] Quality Amendment
- [ ] Response to Administrative Filing Issue
- [ ] Response to Deficiency, Complete Response, Information Request or Additional Comments Letter
- [ ] REMS - Risk Evaluation and Mitigation Strategy
- [ ] Other *(Specify)*:

7. Submission Type *(May select more than one)*

- [ ] Original (New)
- [x] Administrative Amendment
- [ ] Annual Report
- [ ] Letter of Authorization
- [ ] Withdrawal of Letter of Authorization
- [ ] Meeting
- [x] Quality Amendment
- [ ] Response to Administrative Filing Issue
- [ ] Response to Deficiency, Complete Response, Information Request or Additional Comments Letter
- [ ] REMS - Risk Evaluation and Mitigation Strategy
- [ ] Other *(Specify)*:

8. Amendment Type, if applicable *(May select more than one)*

- [ ] Change of agent/address/contact person
- [ ] Change of holder/address/contact person
- [x] Change of DMF Subject (title)
- [ ] Change of DMF Type
- [ ] Meeting Package
- [ ] Meeting Request
- [ ] Controls Information
- [ ] Facility Information
- [ ] Formulation Information
- [ ] Manufacture Information
- [ ] Microbiology Information
- [ ] New Item
- [x] Packaging Information
- [ ] Stability Information
- [ ] REMS Final
- [ ] REMS Assessment
- [ ] REMS Assessment Methodology
- [ ] REMS Revision
- [ ] REMS Modification-Due to Safety Labeling Changes
- [ ] REMS Modification-Major
- [ ] REMS Modification-Minor
- [ ] REMS Proposal-Standard
- [ ] REMS Correspondence
- [x] Agent Appointment
- [ ] Other *(Specify)*:

9. Establishment Information *(Full establishment information should be provided in the body of the DMF. Refer to the instruction sheet for more information. To add additional establishment(s), press button at bottom of section; this may be repeated as needed.)*

Establishment Name
Health Path, Inc.

Establishment Address

Address 1 *(Street address)*
3333 Main Street

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City	State/Province/Region
Buckystown	California

Country	ZIP or Postal Code
USA	20814

Establishment DUNS Number	Registration (FEI) Number
123456789	9876543210

Is the establishment new to the DMF?
☐ Yes ☒ No

Establishment Role *(e.g. manufacturing step, type of testing)*
Manufacturing

Is the establishment ready for inspection? *(See instructions)*
☐ Yes ☒ No If not, when will site be ready? *(See instructions)* 10/25/2021

Establishment Contact *(Name of person)*	Establishment Contact Telephone Number *(Include country code, if applicable, and area code)*
Ms. Jane Doe	301-234-8758
Establishment Contact Email Address	**Establishment Contact FAX Number *(Include country code, if applicable, and area code)***
JaneDoe@healthpath.com	301-234-8700

Click this button to add entries for an additional establishment. May be repeated as needed. **Add Establishment**

Click this button to delete page. May be repeated as needed. **Delete Page**

10. Cross-Referenced DMF(s)

DMF Number 009876 / Subject: Cough Medicine / Holder: XY Pharmaceutical, Inc.

CERTIFICATION

I agree to update this Drug Master File as required in 21 CFR 314.420(c) and notify in writing each person authorized to reference that information. I agree to comply with all applicable laws and regulations that apply to Drug Master Files.

The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be current, true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. Typed Name and Title of Responsible Official	12. Date *(mm/dd/yyyy)*
John Smith, Manager of Regulatory Affaris	12/20/2020

13. Telephone Number *(Include country code, if applicable, and area code)*	(222) 123-4567	14. FAX Number *(Include country code, if applicable, and area code)*	not available

15. Email Address
JSmith@abccompany.com

16. Address of Person Named in Item 11

Address 1 *(Street address or P.O. box, company name)*
ABC Company LLC

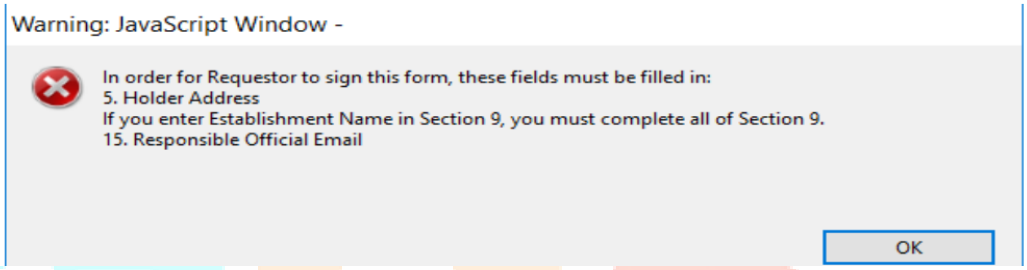
Address 2 *(Apartment, suite, unit, building, floor, etc.)*
2222 Epcot Way

City	State/Province/Region
Laurel	Virginia

Country	ZIP or Postal Code
USA	22046

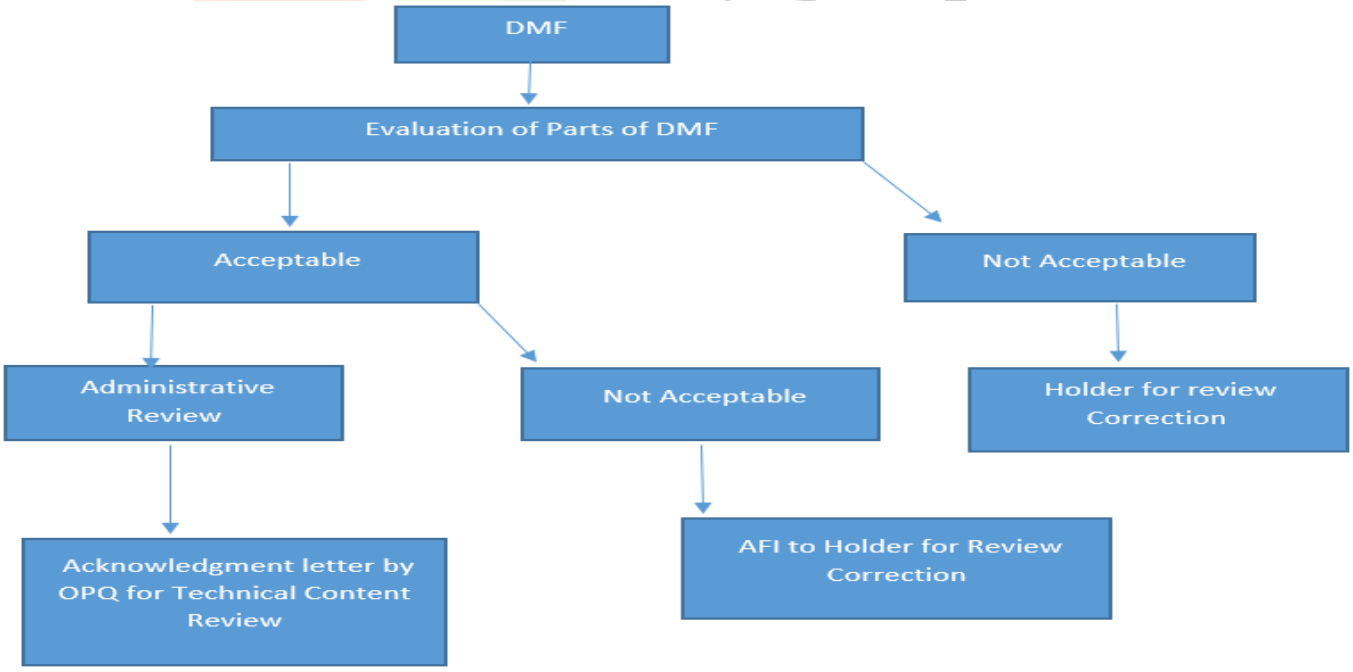
17. Signature of Person Named in Item 11 Sign

Example of Pop-Up Window



1.9) Drug Master File Mechanism:

Before its content can be viewed, DMF must pass two stages of scrutiny. To begin, the FDA examines whether all DMF components are included in the right order. An administrative evaluation of DMF will be conducted after it has been determined to be acceptable. The holder will be alerted if the DMF is really not up to snuff in terms of technology. The holder must reply correctly to any issues in their drug master file before the administrative review may proceed (DMF). The Office of Pharmaceutical Quality (OPQ) will conduct this assessment. OPQ delivers an Acknowledgement Letter when the DMF passes the administrative review and is standard load for technical content examination. An AFI letter is sent to the holder, which requires the holder to account for approximately half of the technical content assessment process. This might take a few of weeks to complete.



1) EU drug master file/ Active substance master file:

2.1) Introduction:

Active Pharmaceutical Ingredients (APIs) are required for the production of pharmaceutical products. Their production makes extensive use of advanced technology. know-how, a large portion of which is intellectual API manufacturer's property as an example, Processes of synthesis, reaction, and purification conditions. Manufacturing data is frequently mislabeled. patents are registered. It is critical to API. Because intellectual property is directly tied to a company's bottom line, manufacturers must take steps to protect it. For a drug product to receive a Marketing Authorization (MA), both the API quality and the end product quality must be validated. Applicant's information on the API can be included with other application data if the applicant generates the API directly. (9)

A third-party API maker is usually responsible for developing APIs rather than the drug product manufacturer. Consequently, API producers are unable to provide applicants for medical products with sensitive information. an ASMF/DMF system is in place to secure the API producer's sensitive data from unauthorized access. (9)

It is possible to protect crucial manufacturing know-how when the active ingredient's producer is not applying for a product marketing authorization through an EC process. Between 1989 and 1991, the company was started. Following the EU's approval of the CTD in 2005, the ASMF (Active Substance Master File) underwent a large change. The ASM Restricted Part of this guideline, which is separated into two sections, solely pertains to active chemicals. Active Substance Manufacturers provide their component of a DMF directly to the applicant, who then files it as part of their marketing authorization request. A part of the DMF dedicated to the applicant as well as the ASM Restricted Section are sent to the appropriate authorities for review. (10)

In 1989-1991, the European DMF was established, and in 2005, it was restructured to become the ASMF (Active substance master file). The ASMF is governed by Directive 2001/83/EC, which was enacted in the EU when CTD was introduced. (11) Both in terms of substance and presentation, the European Union and the United States have quite different requirements. Preserving manufacturer proprietary "know-how" while allowing MA holders to take full responsibility for the product's active ingredient and its quality and quality control are the key goals of ASMF. The European Medicines Agency (EMA) and national regulatory authorities may now more easily assess the acceptability of an active component in a pharmaceutical product. (12)

The ASMF technique is often used when there is a need to preserve privacy between ASM and a potential applicant or MA holder. No active substance information must be included in ASMF form. An application for market approval for a pharmaceutical product may contain this information. (13)

It is possible to prepare the following compounds using the ASMF method, including herbal preparations:

• New active components.

• Drugs and other active compounds that aren't included by the European Pharmacopoeia or one of its member states' European pharmacopoeia.

• Active substances in the pharmacopoeia that are not included by the European Pharmacopeia or a member state's pharmacopoeia (13)

- Applicant Part (Open):

This part comprises all of the essential knowledge, including an elaboration of the production procedure. The application asserts that the information it contains is non-confidential, although the document is open to the public. Allows the applicant to assume complete responsibility for making the decision as to whether or not an active ingredient in a medical product is suitable. Due to the fact that the EDMF holder's permission is required before the applicant component may be made public, it is still kept secure. (11)

- Restricted Part (Closed / Confidential) of ASM:

Active Pharmaceutical Ingredients manufacturing information that is confidential. CTD-format EDMFs must have both summaries in the Quality overall summary type, which contains sensitive information as well as information about specific manufacturing processes such as temperature and validation data for crucial stages. Version numbers for candidates and restricted parts must be distinct and logically structured. (11) In order to determine the suitability of the active ingredient in a medicinal product, the EMEA or the authorised authorities have access to all relevant information. As of July 2016, the EU Directive 2003/63/EC defines the active chemicals for which ASMFs can be submitted, as well as the information required to accompany an ASMF. (11)

- Description of the manufacturing process in detail
- Procedure for quality control during the manufacturing process
- Validation of the procedure

2.1) Active substance master file guidelines:

Applicants for Marketing Authorizations of Medicinal Products in European Union Member States must include all essential scientific evidence from the applicable Notice to Applicants.

1. Guidelines on the quality of herbal medical products have been updated by the European Medicines Agency (EMA) and the Canadian Pharmacopoeia. Ayurveda remedies.
2. The CPMP/QWP/2819/00 and EMEA/CVMP/814/00 recommendations on the quality of herbal medicinal products have recently been updated. products made from herbs
3. A summary of active ingredient requirements' (CHMP/QWP/297/97, EMEA/CVMP/1069/02, in their most recent forms) is included in the dossier's quality section.

Directive 2001/83/EC, Part I, as amended, 3.2 Basic principles and requirements, the Active Substance Master File (for human medicines), and Directive 2001/82/EC, Part I, as amended. General Requirements of C.1 Active Substances (for Veterinary Medicines). (12)

Objectives:

- To assist in the demonstration to regulatory agencies of the quality, safety, and efficacy of a medical product.
- Grant assistance for securing a marketing authority.

Marketing authorization application/ ASMF submission type:

The EMEA must be notified of the applicant's intention to submit an application and given an estimate of when the application will be submitted before an MAA can be submitted. (14)

MAA can be completed in four ways:

Marketing Authorization Application (MAA) for eligible products using the centralized method.

For other items, mutual recognition or national approval are relevant under the decentralized system. (14)

Table no:2.2

Marketing authorization application			
National procedure	Centralized procedure	Mutual recognition procedure	Decentralized procedure
If a company wishes to promote their product in only one EU country, the national method is preferable. Before applying for MAA, the organization must notify the appropriate authorities. To receive national MAA, the organization must submit an application to the appropriate authorities of each member state. Market authorization applications must be completed within 210 days.	This marketing authorization is granted for the whole community market and is valid in the market of all member states. The regulation (EC) 726/2004 establishes a centralized mechanism for the authorization of medical items. There is a single application, a single review procedure, and a single permission permitting direct admission into the community's single market.	This process is preferable; if a firm has market permission in one of the EU member states and wishes to acquire approval in many countries, it may apply for recognition in other EU nations at the same time. It is a more efficient method of reaching the market.	If products do not fall under the purview of the EMA under the centralized procedure, this option is preferable. Using this approach, the manufacturer can seek simultaneous permission in more than one EU jurisdiction for pharmaceuticals that have not yet been approved in any EU country.

2.3) The Active Substance Master File's Content:

Applicants for Marketing Authorizations of Medicinal Products in European Union Member States must include all essential scientific evidence from the relevant Notice to Applicants. (12)

A common technical document (CTD) should be used to describe the EDMF for human medical goods.

After consultation, Competent Authorities/EMEA must receive CTD forms of EDMFs for veterinary medical commodities. An EDMF for a veterinary medicinal product should have the following features: (14)

1. Name and site of active substance manufacturer.
2. Nomenclature.
3. Description.
4. Outline of the manufacturing route.
5. A detailed description of a manufacturing method.
6. Quality control during manufacture.
7. Development chemistry.
8. Analytical validation.
9. Impurities.
10. Batch analysis.
11. Stability studies.

2.4) The filling procedure of ASMF:

MAA or MAV can be supported by an ASMF. MAA or MAV must justify the connection between the active ingredient's quality and its usage in the pharmaceutical product. Although the ASMF technique was created to safeguard the ASM's intellectual property, it is also conceivable to use it when the Applicant/MA holder and the ASM have no confidentiality issues.

For the active chemicals mentioned below, as well as for herbal active substances/preparations, the ASMF technique may be used. Specifically,

A) The introduction of a brand-new active ingredient
B) EU member states' pharmacopoeias and the European Pharmacopoeia (Ph. Eur.) do not yet include active substances.
C) An EU Member State's national pharmacopoeia or the European Pharmacopoeia. C).
(The ASMF procedure is not applicable to biologically active compounds)

Both an ASMF and an EDQM Certificate of Suitability (CEP) are acceptable when it comes to the same active ingredient. An ASMF and a CEP cannot be used for the same MAA/active MAV's constituent at the same time. National Competent Authority/EMA may opt to include extra material in the dossier if the CEP does not have adequate information (for example, stability). ASMFs and CEPs may be called upon in these situations. In order for the National Competent Authority/EMA to analyses ASMF data, the ASMF holder must submit a "Letter of Access" for each MAA/MAV to the ASMF holder. (12)

The EDMF must be sent to the MA holder/applicant by the EDMF holder.

- ✓ Copy of the current version of the applicant's part
- ✓ a copy of the applicant's most recent Quality Overall Summary (QOS)
- ✓ The LOA, if it hasn't been previously filed for the product in question.
- ✓ In the event of an MAA or MAV, the EDMF holder must submit the EDMF to the proper authorities (market authorization variation).
- ✓ when or whether the product has previously received a Letter of Access.

The National Competent Authority/EMA may compel the ASMF holder to produce it for each MAA and MAV, depending on local legislation. There is a one-month limit on the ASMF holder submitting essential documentation to either the National Competent Authority or the European Medicines Agency (EMA).

MA holders/applicants and ASMF holders should submit the MAA and MAV to the National Competent Authority/EMA as part of ASMF procedures if they've not previously done so, along with the Letter of Access.

ASMF holders must provide the same documents to each Member State's National Competent Authority/EMA when the same active component is utilised in multiple applications of different goods. ASMF changes made in conjunction with one MA may be required to be applied across all MAs by the National Competent Authorities/EMA. AP/RP modifications must be reported by ASMF holders to MAs and National Competent Authorities/EMA by contacting MAs and National Competent Authorities, respectively.

2.5) When the ASMF procedure used, the content of the MA dossier changes.

Access to current manufacturing information is required for the Applicant/MA Holder to assume full responsibility and accountability for a medical product's active ingredient's quality. An MA dossier should include the quality assurance criteria used by applicants

and holders of MAs (CTD format sections 3.2.S.4.1 and 3.2.S.4.2).

Applicant/MA holder must provide the same active ingredient specification as the ASMF or CEP holder, unless otherwise justified, if a single supplier is utilised and ASMF or CEP procedure is used.

If the Applicant/MA Holder used a comparable analytical approach to the ASMF, the Applicant/MA Holder must transcribe relevant ASMF portions into its MA dossier to ensure that the relevant sections 3.2.S.4.2 and 3.2.S.4.3 of the MA dossier are appropriately mentioned. The test owner responsible for the method that differs from those specified in the ASMF must certify that method.

In order to support the proposed active ingredient specification, Section 3.2 requests batch analytical data from the Applicant/MA holder, as well as an explanation for the specification. Reference standards are required in 3.2.S.5 by the Applicant/MA holder. Applicant QOS/detailed and critical examination of MA dossier should have AP information. QOS/detailed and critical analysis should identify ASMF concerns that are relevant to the medical device being evaluated. (12)

2.6) what are changes and update to the active substance master file

Every drug must be updated to reflect the most recent synthesis or manufacturing procedure in order for EDMF holders to keep their content current. Without the express consent of the applicant and the responsible authorities, EDMF holders should not make any changes to EDMF material. Before implementing any changes to the EDMF, EMEA should notify the applicant. Every MA holder must submit any changes to the ASMF to the applicable National Competent Authority/EMA via a suitable variation process.

A cover letter should include a detailed list of any modifications. EMEA's cover letter should include the following information.

- A list of all the revisions made since the EDMF was initially submitted.
- Whether or not other member states have approved, refused, or withdrawn their support for the move.
- a new, up-to-date, and comprehensive overview EDMF's old and new materials are directly compared.
- A new version number is assigned to each of the new applicant's parts and restricted portions. (12)

2.7) Overview ASMF module 3 contents:

Part	CTD format/ module	Open part	Restricted part
3.2.S.1	General information	✓	
3.2.S.1.1	Nomenclature	✓	
3.2.S.1.2	Structure	✓	
3.2.S.1.3	General properties	✓	
3.2.S.2	Manufacture	✓	✓
3.2.S.2.1	Manufacturer(s)	✓	
3.2.S.2.2	Description of Manufacturing Process and Process controls	a)	b)
3.2.S.2.3	Control of Materials		✓

3.2.S.2.4	Control of critical steps and intermediates	c)	d)
3.2.S.2.5	Process validation and/or Evaluation		✓
3.2.S.2.6	Manufacturing Process Development		✓
3.2.S.3	Characterizations	✓	
3.2.S.3.1	Elucidation of Structure and other Characteristics	✓	
3.2.S.3.2	Impurities	✓	e)
3.2.S.4	Control of Drug Substance	✓	
3.2.S.4.1	Specification	✓	
3.2.S.4.2	Analytical procedures	✓	
3.2.S.4.3	Validation of analytical procedures	✓	
3.2.S.4.4	Batch analysis	✓	
3.2.S.4.5	Justification of specification	✓	f)
3.2.S.5	Reference standards or materials	✓	
3.2.S.6	Container Closure System	✓	
3.2.S.7	Stability	✓	
3.2.S.7.1	Stability summary and conclusion	✓	
3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment	✓	
3.2.S.7.3	Stability data	✓	

Part	NtA veterinary format	Open part	Restricted part
2.C.1	Name(s) and site(s) of ASM	✓	✓
2.C.1.1	Specifications and routine tests	✓	
2.C.1.2.1	Nomenclature	✓	
2.C.1.2.2	Description	✓	
2.C.1.2.3	Brief outline of the manufacturing route (flow chart)	✓	
2.C.1.2.3	Detailed description manufacturing method		✓
2.C.1.2.4	QC during manufacture	c)	d)
	Process validation and evaluation of data		✓
2.C.1.2.5	Development Chemistry	✓	
	Evidence of structure	✓	
	Potential Isomerism	✓	
	Physiochemical characterization	✓	
	Analytical validation	✓	
2.C.1.2.6	Impurities	✓	e)
2.C.1.2.7	Batch analysis	✓	
2.F.1	Stability	✓	

2.8) EDMF Assessment Procedure:

EDMF assessment processes can be classified as follows based on their link to a related drug product assessment process:

1) Group No. 1 (A drug product evaluation procedure is included in the assessment process.)

2) Group 2 (The evaluation procedure is distinct from the assessment of a drug product.)

Organizations in Group 1 conduct EDMF assessments in combination with drug product assessments (i.e., the EDMF has been cited in a drug product application). The DMF evaluation procedure involves the drug applicant, the EDMF holder, and the regulatory authority. The Applicant's Part/Restricted Part structure is used by all of the companies in Group 1. Non-proprietary content may be shared using this structure since the Applicant's Part is shared by the applicant.

ASMF/DMF evaluation is performed by Group 2 entities independently of the drug product review process. The ASMF/DMF holder or in-country caretaker is responsible for conducting all evaluations in cooperation with the regulatory agency. (14)

Submission Letter and Administrative Details for documents relating to an Active Substance Master File"

From:<ASMF Holder name>

<ASMF Holder address>

<ASMF Holder address>

<ASMF Holder <Post code> Town>

<ASMF Holder Country>

To: <Name and Address of Competent Authority>

<Date>

<Reference>

Subject: Submission of documents relating to an ASMF

for <Name of Active Substance> - < EMEA/ASMF/XXXXX or EU/ASMF/XXXXX[11] or National ASMF reference number> [12]

Dear Sir or Madam:

This Active Substance Master File is submitted in relation to the following product:

Medicinal product	<Name of the medicinal product>[13]
Allocated procedure number (as applicable)	<EMEA/H/C/product reference number/procedure reference> <RMS/H/product reference number/procedure reference> <National Marketing Application/Authorisation Reference>
(Intended) Submission date of the marketing authorisation application or variation (if known)	<DD/MM/YYYY>

Adminisrative details for documents relating to an Active substance master file:

This letter of submission should be used to analyze an Active Substance Master File in conjunction with a marketing authorization application or variation for a human/veterinary medicinal product using a national or mutual recognition, decentralized or centralized system. (12)

This submission is also sent to: (as applicable)	☐ Rapporteur ☐ Co-Rapporteur ☐ All CHMP/CVMP members, as appropriate ☐ RMS ☐ All CMS ☐ <National Competent Authority> only[15]
ASMF reference number	< EMEA/ASMF/XXXXX or EU/ASMF/XXXXX[16] or national ASMF Reference number[17]>
ASMF holder's version (as included in this submission)	Applicants part: Version [version number]/date (dd-mm-yyyy) Restricted part: Version [version number]/date (dd-mm-yyyy)
Active substance name	<INN, common name> (+ salt/water content when applicable)
Active Substance Manufacturer's internal API code (if applicable):	<API internal code>
Additional information (as applicable, e.g. different route of synthesis, grade)[18]	

ASMF Holder	<ASMF Holder name> <Full ASMF Holder administrative address> <Country> Contact person: <name> Telephone: <telephone No.> e-mail: <e-mail>
Active Substance Manufacturer Manufacturing site(s)[19]	<Active substance manufacturer name> <Manufacturing site address(es)> <Country> <D-U-N-S number[20]> <GPS (WGS 84) coordinates of the site[21]> Contact person: <name> Telephone: <telephone No.> e-mail: <e-mail>

Submission Type	☐ New submission ☐ Update to the ASMF ☐ Response to deficiency letter (both Applicant's and Restricted Parts, where applicable) ☐ Administrative change only (manufacturing site remains unchanged in all cases) ☐ Change of ASMF holder ☐ Change of name/address of ASMF holder ☐ Change of name/address of Active substance manufacturer

Submission Format	☐ eCTD[22] - <sequence No.> - [Related Sequence <Related sequence No.>] - ☐ History of the sequences (Sequence Tracking Table) is attached ☐ (V)NeeS ☐ CTD[23] ☐ NtA[24] ☐ paper submission and other electronic format
Number of Volumes of Paper Copy	<Number>
Number of Media Units	<Number>

Submitted Documents	☐ Letter of Access[25] ☐ A copy of the Expert's curriculum vitae ☐ QOS or detailed and critical summary, as appropriate ☐ Table of Changes (only for submission of an update to a currently authorised ASMF) ☐ A copy of the proposed ASMF holder's active substance specification (3.2.S.4.1 or part 2.C.1.1, as appropriate)[26] ☐ A copy of the ASMF Deficiency Letter sent by Competent Authority/EMA (only for submission of response documents) ☐ Correlation table[27] for CTD:NtA formats

Yours faithfully,

<Signature of authorised contact person>

<Name, address and position in company>

MASTER FILE SYSTEM IN JAPAN:

3.1) Introduction:

At the holder's choice, producers of drug substances may register information about their products' quality and production methods with the PMDA using the MF system. (15)

As on April 1, 2005, MF will be applied in compliance with the Revised Pharmaceutical Affairs Law. A pharmaceutical or medical device company's (MF's) primary goal is to ensure that the information essential for an MF's approval assessments (for example, information on manufacturing techniques, etc.) is shared and protected. MF registrant's intellectual property. MF also seeks to make the review process more efficient. After MF goes into effect on April 1, 2005, it will first focus on medical devices and their components. Consideration must also be given to medical devices registered under the Medical Devices Registration Act. Certified bodies might include MF into their certification process, too.

Marketing authorization applicants (MAAs) and holders (MAHs) of pharmaceutical goods are protected from the "know-how" of API production processes by the use of MF. In order to participate in the MF, you should not be forced to form. It is not possible to obtain a certificate of

marketing by registering with an MF agency. When conducting a regulatory examination, the MF records used as relevant information are those that are maintained there. A caretaker in the nation must be selected for products that require authorization of drug substances (APIs), etc., for foreign companies pursuing MF registration. (15)

With MF	Without MF
With MF in this case APIs manufacturer need to contact with the country care taker and give them all the data country caretaker provide you MF registered number and now you protect know how for MAA and then you have to submit only open part to the marketing authorization applicant. MAA applicant submit approval application for pharmaceutical product with the mf registered number to the PMDA.	Without MF in this case APIs manufacturer submit all the CTD open part and close part data to the marketing authorization applicant and then after this all data submit to the PMDA so in this case API manufacture can't protect Their Intellectual Property.

MF registration requires a foreign manufacturer to select an in-country custodian for drug substances when he or she applies (Article 280-3 of the Regulation). As part of the application process, notices and other paperwork should be in Japanese in order to be accepted (Article 283 of the Regulation)

According to the Pharmaceutical Affairs Law Enforcement Regulations, pharmaceutical companies are obligated to follow certain procedures and use specific forms when filing applications to the Pharmaceutical and Medical Devices Agency for MF registration. (15)

3.2) Items to be registered in MF:

In order to make pharmaceuticals and medical devices, the following raw ingredients must be registered with MF.

1. Active pharmaceutical ingredients (APIs) and intermediates (materials of pharmaceutical products with special dosage form, etc.)
2. Existing excipients with a modified composition ratio and new excipients can be pre-mixed in a new formula.
3. Devices made of medical materials.
4. Materials used in packing and containers.

A MF registration is not necessary for drug compounds, intermediates, and pharmaceutical product components used in OTC medications because their quality and safety have already been confirmed by existing specifications (excluding OTC with new active ingredients or active ingredients in the re-examination period).

It is necessary to record BSE measures in MF as part of the BSE measures, as per PFSB / ELD No. 0801001, "TSE Data Number" (PFSB / ELD No. 0801001 Notification by the Director of the Evaluation and Licensing Department / Director of the Safety Division, Pharmaceutical and Food Safety Bureau).

Raw material identifying information is required for products that can be registered in MF for materials used in medical devices. & Items that are recommended for MF registration must be registered in MF during the authorised review procedure. (16).

MF registration:

1. Names of drugs, etc.
2. Name of production site and other relevant details.
3. Ingredients, such as the number and kind of active components or even the nature of the medications themselves, are included in this information.
4. Quality control testing, manufacturing procedure, and process control are all included in this section.
5. Specifications and test methods.
6. An expiration date and tests for stability are included.
7. a study that isn't aimed towards treating patients (mainly for new excipients).
8. Insights on safety problems.
9. manufacturing operations or certification of foreign manufacturers fall into this category.
10. The license number for a manufacturing operation, or the date and time of the foreign manufacturer's accreditation.
11. Information about the applicant's caretaker if the manufacture is located outside of Japan and applying for an MF registration there. (16)

3.3) MF Registration Information Form:

PMDA recognizes MFs for registration if they are properly formatted, such as having the bare minimum of

necessary elements or attaching data (Module 3: in English or Japanese).

It is essential that "Data on Manufacturing Methods and Specifications/Test Methods," "Data on Stability," and "Data on Pharmacological Action" be included in the application form and any accompanying documentation, since these are needed information for the approval of a medicine (pharmaceutical product). For MF registration applications, the registrant must submit Form No. 42 as provided in the Pharmaceutical Affairs Law's Enforcement Regulations.

Notification No. 899 of the PFSB/ELD (dated June 21, 2001) An application for approval to produce or import a new medication will make use of pharmaceutics.

Starting point for generic pharmaceutical forms should be "Approval Application of Pharmaceuticals" (PMSB Notification No. 481, issued April 8, 1999). (16)

Fees and submission of the MF registration application:

The MF does not charge a fee to become a member. To be qualified to take part in the Programme, you must submit a registration form and any supporting documentation to the Administration Division 1, Office of Review Administration (PMDA). When a foreign drug manufacturer is requesting for registration, it is permitted to write the seal on the first page of the MF application form rather than utilize a seal.

The signature of the foreign drug manufacturer's representative is required on the application form. The in-country caretaker's signature and seal are not permitted on an application form.

MF Registration Application Form:

Both the generic and commercial names of the drug substance, etc., must be provided in the name of the drug substance section. Application forms must also contain information that applicants or holders of drug authorizations should have access to (pharmaceutical products).

The registration application form in FD must be submitted. the descriptions in accordance with the "Guidance on the Handling of Applications Submitted on Flexible Disks and Other Media." (March 31, 2005, PFSB/ELD Notification No. 0331023). (16)

Drug substances' production methods must be summarized in an application form, according to the "Guideline for the Descriptions on Application Forms for Marketing Approval of Drugs, etc." (PFSB/ELD Notification No. 0210001, published February 10, 2005).

It is not possible to conduct MF registration (issuing of a number) until the certification/accreditation has been obtained for the manufacturing operation or drug substance production facility, for example. Ensure that you have plenty of time to finish the application process. (16)

3.4) Please see the attachment (registration data):

In order to submit the registration application form, the following forms must be utilised (registration data).

1. The Common Technical Document (as "CTD") attached to "Guideline on Preparing Data Attached to Application Form for Approval Application of Manufacture or Import of a New Pharmaceutical" (PFSB/ELD Notification No. 899, dated June 21, 2001) shall be used for pharmaceuticals excluding generic drugs and OTC drugs. At the time of MF registration, the data equal to Module 2 of CTD (Summary of the Attached Data) is not required. PMDA reviewers in charge of the drug's approval review will direct the time of submission (pharmaceutical product). Electronic forms for MF registration must meet with the "Electronic Specifications on Common Technical Documents" (PFSB/ELD Notification No. 0604001, issued on June 4, 2003 by the Director of the Pharmaceutical and Food Safety Bureau's Evaluation and Licensing Division).
2. The "Approval Application of Pharmaceuticals" (PFSB Notification No. 0331015, dated March 31, 2005) should be followed for drug compounds used in generic pharmaceuticals.
3. Excipients and pre-mix ingredients with a different composition ratio than the present ones" and "Containers/packaging materials" must adhere to the "Application for Approval of Non-Prescription Pharmaceuticals" for the drug substance used only for OTC (PFSB Notification No. 0827003, dated August 27, 2003). (16)

3.5) MF Registration Certificate Issuance and Publication:

Post-registration, the applicant will be provided with Form No.121 of the Regulation, which serves as both a certificate and a copy of the registration application form, confirming their status as an MF. The registration certificate does not include any sensitive information.

On the PMDA's website in the near future, you will be able to find out the MF registration number and registration date, as well as the registrant's name and address. (16)

3.6) Procedures for MF Registration:

1. New registration:

The Application of (Original 1, Duplicate 1; Duplicate must not be a Xerox copy of Original)

MF registration data (including CTD Module3) is only available electronically. (15) If you are registering for the first time, you must send the PMDA your completed application form and any supporting documentation you have. Categories of registration may be seen here.

- To be used only in the production of medicinal products. There are a number of ways to create drug substances (i.e., drug substances, intermediates, and pharmaceutical product materials) (except those intended solely for use on animals).
- pharmaceutical product excipient compositions or excipients with a different composition ratio than those now in use are under development (refers to novel excipients and pre-mix excipients with a different composition ratio than existing ones, respectively).
- Medical-grade materials that can only be used in the production of medical products (excluding those designated purely for animal use) Other (packaging material, etc.)

The application form for registration must include a summary, of the manufacturing procedures to be registered. Fill out the form in accordance with Notification No. 0210001.

Consult Form No. 43, Pharmaceutical Affairs Law Enforcement Regulations, for further information on the registration certificate (see below), as well as the registration application. The certificate of registration does not contain any private information. (16)

2. When a new approval application is created using MF:

The name and registration number of MF, as well as the date and number of changes to their registration certificate, must be included in pharmaceutical product applications. Applicant must submit their registration certificate and an agreement to utilize MF to the MF registrant.

Notifications addressing the procedure for utilizing MF in medical device approval applications must be supplied separately.

During approval reviews, PMDA shall make direct enquiries to the MF registrant regarding materials registered in MF. Such queries must also be communicated to the applicant who submitted the relevant permission application by PMDA. (16)

3. Changes to registered items:

To update the registered material in the MF database, the MF registrant must submit an application whenever an FDA product approval review asks for modifications (changes). Following that, when the related application of pharmaceutical product is authorized, the registration certificate for that change will be granted.

An application for updating the registered materials, as well as the accompanying data, must be submitted to PMDA when adjustments are made to registered contents. The only changes that need to be reported are those that affect the data that is relevant to the situation. The modifications made to the registered items may necessitate the filing of a new registration rather than a change application in some situations. Firm name, approval number, the licensee's name and location, and if a minor change application or notice was submitted for making changes to registered content in MMF are all required information when making changes.

All previously authorised pharmaceutical goods that use the modified MF must have a partial change approval application filed along with a request to update the MF's recorded contents.

Modifications to MF-registered things must specify whether or not the existing items are still being used for previously approved pharmaceuticals. Adding a new manufacturing method, for example, requires that both the present and newly added manufacturing methods be numbered so that the pharmaceutical items certified by mentioning the MF may be identified by these written numbers. Pharmaceutical goods with added items and those with existing items must both be updated in the database when filing an application to alter the contents recorded in MF.

It is necessary to file an application for partial change permission for pharmaceutical goods that use certain MFs in order for these products to quote newly registered items rather than a change of registration if MF alterations would substantially affect the nature of therapeutic ingredients, etc. If the changes are substantial and the items are not deemed to be the same, a new approval application should be filed by the approval holder of pharmaceutical products. It is thus recommended that modifications be reported to the review authority.

No matter how much time the registered material is revised, it will still be handled in accordance with the date the modified registration certificate was issued. (16)

- Minor change notification:
- Notification of Minor Changes (Original 1)

• Data from the MF Registration Application (including CTD Module 3); where needed
• Declaration (appropriate validation, change control, etc.
• Other (Comparison table, old/new, etc.) (15)

To update the registered material in the MF database, the MF registrant must submit an application whenever an FDA product approval review asks for modifications (changes).

I. The nature, properties, performance, and safety of the medication ingredient, for example, might be affected by changes in production procedures.
II. Elimination of items from the requirements and test methods, as well as revisions to the specifications.
III. Changes in the removal or inactivation of pathogens.
IV. Any alterations that might have an influence on the product's quality, effectiveness, or safety are prohibited.

Modifications in registered items must be notified within 30 days of the changes being made to PMDA in order to ensure proper validation and change control in accordance with PMDA regulations (see "Documents to be Submitted").

This data must be given to the applicants and holders of authorization for medications using the MF as part of the minor modification notice. (16)

9. Partial Change Approval Application for Drug (Ph
    - Application (Original 1, Duplicate 1; Dupli
    - Data of Application for MF Registration (i
    - Original Registration Certificate.
    - Other (Old/New Comparison table, etc.) (1

A partial change approval form must be filed together with the modification request for the registered goods if the MF under consideration is referenced in previously approved pharmaceuticals (pharmaceutical products).

To begin an evaluation of the registered goods, all partial change applications for the relevant medications must be filed. As soon as these adjustments are approved, PMDA will issue the MF registration certificate, containing the updated registration date, etc., for the change.

Once an MF item has been modified, it must be mentioned if it is needed by a drug that was previously approved. By way of example, every company that wishes to have their pharmaceutical products certified by the MF must number both the existing and newly additional production processes. Medication marketing authorization holders (pharmaceutical goods) are needed to submit applications for new items and minor modification notices for existing products that are getting slight alterations in this case. (16)

4. Cancelation of MF:
    - Notification (Original 1)
    - Statement (confirming that there is no product using the MF number to be cancelled)
    - Original MF Registered Certificate (15)

Approval Application and Review for Drugs (Pharmaceutical Products) Quoting MF:

a. When the MF registration is finalized.
Enter the name of the drug substance, etc., its MF registration number, the most recent issue date of the registration certificate, and the number of times the registration certificate was revised in the manufacturing methods section of the approval application form. Enter "1" for the first registration, and then add 1 for each subsequent revision. The number, however, does not change for the minor change notification. If more than one manufacturing method is registered in a single MF, indicate which method is being used.
A copy of the MF registration certificate and a copy of the contract with the MF registrant for the use of the MF shall be considered as part of the documents when applying for approval of a drug (pharmaceutical product).

such as "Data on" to be attached to the approval application for Data on Manufacturing Methods and Specifications/Test Methods" and "Data on Manufacturing Methods and Specifications/Test Methods Stability". (16)

b. Awaiting conclusion of the MF registration.
A drug (pharmaceutical product) application can be filed using the system receipt number issued at the time of application and marking in the application form that "MF registration is in progress" if the MF registration application has been submitted.
Contact the Office of Review Administration as soon as the MF registration is complete and request that the approval application be reposted. Drug (pharmaceutical product) approval review cannot begin until an approved application with an updated MF number is submitted.

c. Approval review for drugs.
During the pharmaceutical approval review process, PMDA contacts the MF registrant directly if there is a question about the MF registered products (if the MF registrant is a foreign manufacturer, the inquiry will be made through the in-country caretaker).
If the review results in any modifications to the registered items, a request for a change in registered items or a notice of a minor change notification must be submitted as soon as possible. As soon as a new medicine is authorised by the FDA, the PMDA provides a new registration certificate for any registered item that has experienced a change. The

registered items cannot be modified if just the associated document has been altered.

Based on the registered item and its content, it may be necessary to apply for a new MF registration rather than a modification in registered items application (for example, when the adjustment may impact the nature of the drug ingredient, etc.). A proposal may be needed of you. (16)

3.8) In-Country Caretakers' Responsibilities for Drug Substances:

Due to Article 283, which requires that all documents pertaining to MF registration must be written in Japanese, those who are tasked with delivering medication in their home countries play a crucial part in the administration process. A medicine's approval evaluation may include questions about MF-registered products (pharmaceutical product). A caretaker in the country of origin will contact the MF registrant on behalf of PMDA rather than directly. The in-country caretaker is the primary point of contact for any questions or administrative issues that may arise following your registration.

The in-country caregiver and the MF registrant should work together to carry out these duties. There is a possibility that in-country careers could be replaced. Please notify us if the caretaker in the country has changed, even if there is a slight change. (16)

Transfer of Registration:

In order to properly execute these responsibilities, the in-country caretaker should cooperate with the MF registrant. Documents related to the registration process, including any agreement between the transferor and the transferee, should be supplied during the transfer process. Another need is the production site's or other manufacturing technology's certification that no alterations have been done, etc. (16)

3.9) Summary of the Master File System:

There must be a thorough understanding of Japanese law and instructions for the MAA/MAH, the MF Holder, and any carers in Japan.

The portion that has been made public. MF owner, MAA/MAH, and the person in charge of the host nation must all be in contact.

restricted (closed) area of the website The holder of the MF and the person in charge in the host country must stay in contact. (15)

CTD module open part and close part

Section	CTD Module 3 specification	Open part	Close part
3.2.S.1	General Information (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	Controls of Critical Steps and 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	Characterizations (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	Validation of Analytical Procedures (name, manufacturer)	✓	
3.2.S.4.4	Batch Analyses (name, manufacturer)	✓	✓
3.2.S.4.5	Justification of Specification (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)	✓	

Note: Both the restricted and the disclosed parts are essentially exposed. However, information about the MF holder's intellectual property may not be disclosed. (15)

Research methodology:

Sr no	DMF requirement	USFDA	EMA	PMDA
1	Health Authority	U.S. Food And Drug Administration	European Medicines Agency	Pharmaceuticals and Medical Devices Agency
2	Definition of Drug master file	ASMF protocol, formerly known as the European Drug Master File (EDMF) method, aims to protect proprietary intellectual property or "know-how." Applicant or Marketing Authorization Holder, on the other hand, has complete responsibility for the medical product.	The ASMF system prioritises the preservation of sensitive intellectual property or "know-how," which was previously known as the European Drug Master File (EDMF) standard. The Applicant or MA might, however, assume complete liability for the medicinal product.	The "know-how" of API manufacturing procedures is protected in a master file by pharmaceutical marketing authorization applicants (MAAs) and holder (MAHs).
3	Type of Drug master file	Four Types of DMF: Type II: Material used to make a drug, intermediate drug substance, and final drug product Type III: packaging Type IV: Ingredients, Colorants, Flavors, Essences, or Substances Used in the Manufacturing Process Type V: FDA Accepted Reference Information	The drug master file does not have a type.	There is no such thing as a master drug file type.
4	Format	USFDA requires two copies of each kind of DMF in CTD format, but not in CTD Module format. The CTD format is required by the FDA for all continuous documents. In addition, QOS is required. Submissions may be made electronically or by paper.	QA and QOS in CH CTD Module 3. Application Part (AP) and Restricted Part (RP) of ASMF. A physical and electronic copy must be provided in order to be accepted by the Netherlands, while France demands both. As with the paper version, the electronic version of the DMF must be accompanied by appropriate application forms in France. These documents are required. Several additional nations are in the	Xerox copies of the original application are not acceptable as a copy. PMDA wants Application, Original 1, Duplicate 1. Applicant for MF Registration, as well as CTD module 3. CTD Module 3 can only be completed online.

			process of switching to an electronic filing format other than ICH (Xml) and non-eCTD. Belgium, Denmark, Germany, and France are examples of these country.	
5	Submission name	Drug master file	Active substance master file	Master file
6	Use of DMF support of application	An investigation into the use of a new medication Abbreviated new drug applications and other export applications are all included in the new drug application process.	Marketing authorization application through, Centralized procedure, Decentralized procedure, Mutual recognition procedure, and national procedure	Pharmaceutical and medical device application
7	Language	must submit an exact and full 'English' translation	English	Japanese and English
8	Is it mandatory	Not by law	Not by law	Not by law
9	Submission Type	eCTD format required	eCTD format require	Ectd format required
10	Submission type in CTD format	Required	Required	Submission in Indian CTD format
11	Forms for DMF filling	Type III DMF using Form 3794 is the only exception.	Not required	Form no 42 is used
12	Provide information	The raw material used to make a drug substance, an intermediate drug substance, and a completed drug product. Material used to package products, Preparation material or ingredient that is employed in their formulation. References recognised by the FDA	Compounds that have been offered a new purpose. There are medications available on the market that are not included in the European Pharmacopoeia or the national pharmacopoeia of an EU member state, yet they include active pharmacological ingredients.	Components of pharmaceutical goods, including drugs and intermediates (medicines with unique dose forms, and other pharmaceutical materials.) Use a variable composition ratio for new excipients and for pre-mixing existing ones. For medical devices, the materials needed. Materials for packing and storing
13	DMF number Assigned by reviewers	Yes applicable	Not Applicable	Yes master file registration number
14	Approved Disapproved by Regulatory Authority	Not mandatory nor approved only accepted along with other application	Only accepted	Only accepted
15	Deficiency letter	Yes applicable	Yes applicable	Yes applicable

16	Changes and approved	Yes accepted	Yes accepted	Yes accepted
17	Appointment of in country caretaker	Applicable	Applicable	Mandatory
18	Latter of Authorization	Yes required	Yes required	Yes required
19	Closure or Withdrawal	Yes applicable	Yes applicable	Yes applicable
20	Reactivation	Yes applicable	Yes applicable	Yes applicable
21	Submission along with DMF	Letters of Transmittal In Section III, the DMF type and the subject of the submission are defined. A list of all sponsors, applicants, or holders, as well as any relevant document numbers, should be included with the DMF if the application is known. The signature of the holder or the representative authorised to act on their behalf. Typed in the Signer's Name and Title. People and their locations are listed below: 1) DMF Holder 2) The headquarters of the business 3) Manufacturing Processing Facility. 4) Make contact with the FDA. 5) Agents, if there are any. b. the exact assigned duties to each of the individuals specified under Section A's several categories.	Include a copy of the MA Holder's letter of access to their MA/MAV application as an annexe. Form for submitting information to the NCA/EMA and updating an ASMF with the same data each time. The applicant's share. The restricted area. The Applicant's and Restricted Parts' Quality overall Summary (QOS) Curriculum Vitae of an Expert.	Administration Division must receive the registration application form and any attachments. A handwritten signature by the representative may replace the seal on the application form, which can be completed in their native language on the front page (seal).
22	Require CTD module	Module 1,2 and 3 must be required	Only module 3 required	Only module 3 required
23	Document type (eCTD/PDF)	eCTD	eCTD	PDF/FD(flexible disc)

24	Review time	Assessment must be completed within 60 days of payment. 6 to 8 months for the scientific evaluation process.	10 to 11 month required	6 to 7 month require
25	Life cycle management (amendment/annual report)	Major changes – tell and do; Amendments. Annual reports/updates/amendments are also supplied with minor adjustments.	Without the express consent of the applicant and the responsible authorities, EDMF holders should not make any changes to EDMF material. Before implementing any changes to the EDMF, EMEA should notify the applicant. Every MA holder must submit any changes to the ASMF to the applicable National Competent Authority/EMA via a suitable variation process.	The MF registrant must submit an application to alter the registered items in MF if changes are required as a consequence of approval reviews for pharmaceutical goods. Registration certificates will be supplied once the appropriate application for a pharmaceutical product has been approved.

Summary:

It is critical to include the drug master file (DMF) when presenting a document to a government agency such as the FDA, the European Medicines Agency, or the Japanese Health Workforce Welfare and Labor Ministerial Office (MHLW). [(1)] Drug Master File: What is it? Drug master files, which contain information on the facilities, techniques, or items used in the creation, processing, packaging, and storage of human-use pharmaceuticals, are accepted voluntarily by the FDA. When proposing a drug to a certain market, a pharmaceutical company often creates this paperwork. Information on any active pharmaceutical ingredient (API) is readily available online, as well as about the medicinal substance, the drug carrier, and the packaging material. Companies are growing power to sponsors or applicants who support an FDA application can be done using these files without the DMF holder providing any information to such sponsors or applicants. (1) All of the information regarding an API or Finished Drug substance may be found in a DMF. This phrase is known by a variety of names across the world. If you're from the US, you've likely heard of the US Drug Master File (US-DMF), the European Drug Master File (EDMF), or the Active Substance Master File (ASMF). There are multibillion-dollar potential profits and hundreds of thousands to millions of dollars in research and development time associated with medication applications that are supported by DMFs. The CMC of a drug product's component, such as the drug ingredient, excipient, or packaging material, is typically covered by DMFs. A DMF can contain drug product information as well as non-CMC information (e.g., facilities, toxicology). (1) The DMF is required for drug product registration in the vast majority of nations throughout the world. Information from the CMC sections of the drug submission is included in DMFs to represent the drug's identity, potency, purity, and quality as well as other characteristics. From highly regulated markets (HRMs) to nearly regulated markets, (NRMs) the DMF procedure is used all over the world. HRMs, such as the United States, the European Union, Japan, Canada, and Australia, employ DMF methods entirely, but NRMs, such as Brazil and Russia, and South Africa, do not. for example, use a system known as a technical package. There is no DMF in less regulated markets (LRMs). India is categorized as an LRM and lacks both a DMF system and a technical package. (2) They've been addressed in a number of worldwide guidelines produced by regulatory authorities such as the FDA, EMA and the Australian Therapeutic Goods Administration, who are all concerned with addressing issues. (2)

Conclusion:

The Medicinal Master File contains accurate and comprehensive information about the qualities and manufacturing processes of a drug product. Human-made items include the packaging and cGMP status of any drug. To get marketing authorization, the structure and content of the Drug Master File are employed. As a pharmaceutical product's quality, safety, and efficacy are demonstrated in a DMF, it is the primary goal of the DMF to meet regulatory criteria. This aids in the process of obtaining a marketing license. Now, beginning in 2016, The vast majority of regulated nations will use eCTD or similar technologies to submit DMFs electronically. With the greatest care and sensitivity, API dossier (Drug Master File) clearance should be handled. API registration processes should be thoroughly explained. Drug product applications often need the assistance of the Drug Master File (DMF). The drug product application will be affected if any changes are made to the approved DMF.

In support of many applications to bring the medicine to market, the master file for the drug was reportedly submitted. Drug ingredients, drug products, intermediates employed in their preparations, and so forth are all subject to chemical manufacturing and controls (CMC). The drug master file is not required to be lodged in any specific country. Each country has its own set of rules and regulations in place when it comes to the submission of the drug master file (DMF). As a consequence, global standardisation of DMF filing will become necessary in the future.

ACKNOWLEDGEMENT:

Authors express their sincere thanks to dr. K.S salunkhe for quality guidance and also thanks to Sanjivani college of pharmacy for providing good facilities.

References

1. *Drug master file filing in US, Europe, Canada and Australia.* **Indu Gurram, M.V.S. Kavitha, Nagarjuna reddy, M V Nagabhushanam.** 2, s.l. : journal of pharmaceutical Research , 2017, Jornal of pharmaceutical Reaserch , Vol. 16. 116432.

2. *DMF FILING IN US, EUROPE AND CANADA.* **Agarwal Pooja, Badjatya J.K.** 4, s.l. : international journal of Drug Regulatory affairs, 2015, Vol. 3. 23216794.

3. *FDA. Drug master files guidance for industry.* **(FDA), F.** October, s.l. : FDA, CBER, CDER, october 2019, Vol. Revision 1. 2404022733.

4. **Gajendra singh, Gaurav agarwal, Vipul gupta.** *Drug regulatory affairs.* bengaluru : CBS publication & distributors, 2020. 9788123928814.

5. **sachin Itkar, Dr.N.S. Vyamahare.** *Drug regulatory affairs.* pune : Nirali prakashan Advancement of knowledge, 2020. 9789380064680.

6. **freyr.** *Drug master file (DMFs) in eCTD Format and the FDA key updates you should be aware of.* s.l. : freyr global regulatory solutions & services, March 12, 2018.

7. *DRUG MASTER FILE: GLOBAL REGULATORY ISSUES AND CHALLENGES.* **pankaj kumar, Bharti mangla, satbir singh, and arpana rana.** 01, new delhi : European journal of biomedical and pharmaceutical scinces, 2017, Vol. 5. 2349 8870.

8. *DMF filling procedure in US, Europe and canada: A litrature Review.* **chakraborty, Krishnasis.** 2, Bangalore : International journal of drug regulatory affairs, 2020, Vol. 8. 2321 6794.

9. *Guidline on Active substance master file procedure.* **EMEA.** april, Europe : EMEA/CVMO/134/02 REV 1, 2018, EMEA/CVMO/134/02 REV 1, Vol. 44. 134.

10. *Filling of DMF in the US, EU, and India and its comparative review.* **Veera kota lakshmi sravanti, Ruchita bandha, Ravi kumar reddy juturi.** 1, bhimavaram : International journal of drug rgulatory affairs , march 15, 2021, International journal of drug regulatory affairs , Vol. 9. 2321 6794.

11. *Guidance on Drug master file system in japan.* **PMDA.** s.l. : PMDA, 2015.

12. **Director of Evaluation and licensing division, pharmaceutical and food safety bureau, ministry of health labour and welfare.** *Guidline on Utilization of Master file for drug substance,etc.* s.l. : PMDA, 2007. 0619004.

13. **freyr.** Overview on DMF/CEP -need of regulatory submission. *www.fyeyrsolution/Blog.com.* [Online] freyr Global solutions & services, july 4, 2014. https://www.freyrsolutions.com/blog/overview-dmf-cep-regulatory-submission.

14. **USFDA.** drug master file (DMF). *offical website of united state government.* [Online] U.S food & drug administration, 08 20, 2021. https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs.

15. *regulatory requirements of drug master files by food and drug administration (USA), European medicines agency (Europe) and health canada(canada) and their comparison.* **M.vaseem akram, D. nagarjun, M. nagabhushanam, B. venkateswarlu.** 3, Guntur : Journal of Global trends in pharmaceutical sciences, 2014, journal of Global trends in pharmaceutical sciences , Vol. 5. 22307346.

16. *Similarities and diffrences of international practices and procedures for the regulation for active substance master file/drug master files of human use: moving toward regulatory convergence.* **maki matsuhama, tomoko takishita, ryosuke kuribayashi, kazunori takagi, rika wakao and kenichi mikami.** 2, tokyo : J pharm pharm science, august 5, 2016, Vol. 19. 290 300.