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Research

SIMILARITIES AND DIFFERENCE BETWEEN US DMF, CANADIAN DMF AND EDMF

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Abstract

Purpose: The submission of a DMF is not required by law or FDA regulation, it is submitted solely at the discretion of the DMF holder. The DMF contains factual and complete information on a drug product's chemistry, manufacture, stability, purity, impurity profile, packaging, and the cGMP status of any human drug product. The present work gives the Detailed idea on how to file Drug Master File in US, EUROPE, CANADA, AUSTRALIA.

Approach: A Drug Master File is a submission of information to the FDA to permit the FDA to review this information in support of a third party's submission without revealing the information to the third party. In US, DMF filing was done through NDA for drugs, ANDA for generics and BLA for Biologics. In Europe, DMF filing was done through MAA via centralized procedure for eligible products and for other products via decentralized procedure was used. In CANADA, DMF filing was done through NDS for both drugs and biologic products, where as in AUSTRALIA different application processes and regulatory requirements apply depending on the type of therapeutic goods that is applied.

Findings: This gives you clear vision on how to file Drug master file in US, EUROPE, CANADA and AUSTRALIA. This paper also gives you the comparison of DMF fling procedure in the above-mentioned countries so that reader can have clear idea on how to file DMF and different concerns on DMF among the above counties.

Conclusion: The DMF contains factual and complete information on a drug product's chemistry, manufacture, stability, purity, impurity profile, Packaging and the cGMP status of any Drug product for humans. The content and the format for Drug Master File is used to obtain marketing Authorization. The main objective of the DMF is to support regulatory requirements of a medicinal product to prove its quality, safety and efficacy. This helps to obtain

	a marketing authorization grant. Now from 2016 onwards most of the regulated countries will use eCTD or their electronic format for their DMF submission.
	Keywords: DMF, FDA, CDR, CMC, CEP, LOA, TGA, ACPM, ACSOM, NDS, MAA, ANDA A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.

INTRODUCTION

Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, 1 packaging, and storing of one or more human drugs .

DMFs usually cover the Chemistry, Manufacturing and Controls (CMC) of a component of a drug product e.g. drug substance, Excipients, packaging material. Drug product information or non-CMC information may be filed in a DMF.

A DMF is required to supply bulk Drugs to the United States but the FDA does not require all manufacturers to submit a DMF. However, the information contained in a DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an Export Application, or related documents.

Before going to the details of DMF submission in different countries, an understanding between differences prevailing in Application procedures and DMF are given below :

POINTS TO BE NOTED IN THE PROCESS OF DMF SUBMISSION :

DMF Does not come under regulatory status as it is not mandatory to file it.

- DMFs are entered into database as per their types. (Separate database for each type of DMF).
- Submitted to Central Drug Registration (CDR).
- No assignment to a reviewer, no due date.
- DMFs are reviewed only when referred by an application or DMF.
- If the anniversary date for annual update is missed FDA will not send a reminder.

Types of DMF Submission:

Therapeutic goods can be very beneficial, but to be effective they must be modified the way they work on body systems. This means there are risks, as well as benefits, associated with their use. Because of these risks, these products must be regulated in order to protect public health.

The following information gives you an idea of Drug submission types in US, Europe, Canada and Australia.

USA:

- New Drug Application (NDA), for new drugs.
- Abbreviated New Drug Application (ANDA)-for generics.
- Biologic License Application (BLA), for biologics .

EUROPE:

- Marketing Authorization Application (MAA) via the centralized procedure for eligible products.
- For other products, via the decentralized, mutual recognition or national authorization are applicable

CANADA:

New Drug Submission (NDS)

for both drugs and biologic products.

AUSTRALIA:

- Different application processes and regulatory requirements apply depending on the type of therapeutic good that is to be supplied.
- The Australian Regulatory Guidelines for Prescription Medicines (ARGPM) will assist sponsors to prepare applications to register new prescription or other high risk medicines for human use in Australia.
- The Australian Regulatory Guidelines for OTC Medicines (ARGOM) will assist sponsors to prepare applications for a new OTC medicine for human use in Australia.
- The Australian Regulatory Guidelines for Complementary Medicines (ARGCM) will assist sponsors to prepare applications for new complementary medicine for human use in Australia.
- The Australian Regulatory Guidelines for Medical Devices (ARGMD) will assist manufacturers and sponsors of medical devices in meeting the regulatory requirements for legally supplying a medical device in Australia.
- The Australian Regulatory Guidelines for Biological (ARGB) will assist sponsors to prepare applications to register a new biological for human use in Australia.
- Another therapeutic good (OTG) includes things such as disinfectants and tampons.

DMF types:

Master Files (DMFs) are required in most countries as supporting documents for the registration of drug products. DMFs generally contain information pertaining to the chemistry , manufacturing and controls (CMC) sections of the drug submission and reflect the drug's identity, strength, purity and quality.

The DMF procedure exists all over the world, from highly regulated markets (HRMs) through nearly regulated markets (NRMs). The HRMs, such as the US, EU, Japan, Canada and Australia, exclusively use DMF procedures, whereas NRMs, including Brazil, Russia and South Africa, utilize a system called a technical package. In less regulated markets (LRMs), no DMF procedure exists. For example, India, which is classified as an LRM, has neither a DMF system nor a technical package.

All these issues are covered by guidelines, published by the various international regulatory authorities such as the US Food and Drug Administration, European Medicines Agency, Australian Therapeutic Goods Administration, Canadian Health Protection and Foods Branch and several others.

US DMF – TYPES

Type I-Manufacturing Site, Facilities, Operating Procedures, and Personnel. This is no longer accepted by the FDA.

Type II – Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product

Type III – Packaging

Type IV – Excipients, Colorant, Flavour, Essence, or Material Used in Their Preparation

Type V – FDA Accepted Reference Information Used for sterile manufacturing plants and contract facilities 3 for biotech products .

US DMF Filing System

Filing the DMF

- ✓ Holder sends two copies of the DMF to FDA
- ✓ DMF is reviewed for administrative purposes only by Central Document Room staff.
- ✓ DMF entered into database, assigned a number and acknowledgment letter sent to holder
- ✓ A DMF is neither approved or disapproved

Accessing the DMF: Letter of Authorization (LOA)

- The DMF will be reviewed only when it is referenced in an Application or another
- The Holder must submit two copies of the LOA to the DMF, plus a copy to the Applicant.
- The Applicant submits a copy of the LOA in their Application.
- The LOA is the only mechanism to trigger a review of the DMF by the FDA.

DMF Review Procedure

- ✓ The DMF is reviewed only if referenced by an Applicant or another DMF
- ✓ If the reviewer finds deficiencies in the DMF, the deficiencies are detailed in a letter to the Holder.
- ✓ The Applicant will be notified that deficiencies exist, but the nature of the deficiencies is not communicated to the Applicant.

Format, Font, Font Size and Paper used for submission to USFDA

- ➢ Electronic DMF should be filed. In Common Technical Document, the display of information should be unambiguous and transparent, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents.
- ➢ Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (E.U. and Japan) and 8.5 x11" paper (U.S.). The left-hand margin should be sufficiently large that information is not obscured by the method of binding. Font sizes for text and tables should be of a style and size that are large enough to be easily 4 legible, even after photocopying .
- ➢ Times New Roman, 12-point font is recommended for narrative text. Every page should be numbered, according to the granularity document. Acronyms and abbreviations should be defined the first time they are used in each module.
- ➢ DMF neither approved nor disapproved by USFDA.
- ➢ U.S. standard paper size (8.5 by 11 inches) is preferred.
- ➢ Paper length should not be less than 10 inches nor more than 12 inches. However, it may occasionally be necessary to use individual pages larger than standard paper size to present a floor plan, synthesis diagram, batch formula , or manufacturing instructions. Those pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved.
- ➢ The agency's system for filing DMF's provides for assembly on the left side of the page. The left margin should be at- least three fourths of an inch to assure that text is not obscured in the fastened area. The right margin should be at least one half of an inch. The submitter should punch holes 8 1/2 inches apart in each page.

AIM AND OBJECTIVE

Pharmaceutical manufactures need to prepare a document and submitted solely at its discretion to the appropriate regulatory authority in the intended drug market. The file is known as the DMF in US and EDMF in EU the work into compare the drug master files between USFDA and EU for drug registration process and also vision to gain the research about Para IV filling in US and IPR in EU which is useful for the knowledge on drug patents.The literature work, the comparison parameters, difference in filing process of DMF and EDMF requirements has been studied and explained in detailed in this work, which gives the clear over view of the role of filing the DMF and EDMF. It also gives an outline work of PARA IV filings and IPR Studies.

DISCUSSION

DMF Filing Procedure

According to 21 CFR 314.420, Applications for FDA Approval to Market a New Drug, the FDA discusses requirements for submitting a DMF. The DMF should be in the English language. Whenever a submission contains information in another language, it should be accompanied by a certified English translation.

Aside from the User Fee Form, no other forms should be filled out or submitted along with a DMF submission. Letters of Authorization (LOAs) submitted with initial DMF submission must contain the DMF number. Each page of each copy of the DMF should be dated and consecutively numbered and any updates should include an updated table of contents.

DMF submissions should include.

⎫ Transmittal letter

⎫ Administrative information, and

⎫ The specific information involved in the DMF.

The transmittal letter for an original DMF should cover the following:

¬ Identification of submission: Original, the type of DMF, and it's subject;

¬ Identification of the applications, if known, that the DMF is intended to support, including the name and address of each sponsor, applicant, or holder, and all relevant document numbers; ¬ Signature of the holder authorized representative or agent;

¬ Name and title of the signer.

The administrative information required is as follows.

The names and addresses of the following must be provided.

¬ DMF holder; ¬ Corporate headquarters;

¬ Manufacturing/processing facility;

¬ Agent(s), if any;

¬ Contact for FDA correspondence; this is the contact person and a telephone number;fax number and email address should be provided;

¬ The specific responsibilities of each person;

¬ A statement of commitment; ¬

A signed statement by the holder certifying that the DMF is current and that the DMF holder will comply with the statements made in it.[2]

To ensure DMFs are current, the FDA sends "Overdue Notification Letters" to companies that do not submit a report every three years. The holder has 90 days in which to respond and submit its annual report. If they fail to respond, their DMF may be closed.[7]

Letter of Authorization DMF

holders must submit a letter of authorization to FDA in support of an application permitting the FDA to reference the DMF.

It should include;

¬ Date

¬ Name of DMF holder

¬ DMF number

¬ Name of person authorized for incorporating information in the DMF

¬ Specific products covered by DMF

¬ Section number & page number to be referenced

¬ Statement of commitment that the DMF is current & that the DMF holder will comply with the statements made in it.

¬ Signature of the Authorized person.

DMF Filing, Assessment & Review

¬ DMF holder should send two copies to FDA

¬ Then DMF is entered into the database system, a number is assigned, and an acknowledgement letter is sent to the holder.

¬ A DMF won't be reviewed unless it is referenced with an application, so the applicant should include a copy of their letter of authorization in their application as it is the only way to trigger the FDA's review of the DMF.

¬ If the reviewer finds any deficiency the reviewer will issue a letter to the holder statingthe deficiencies but will not describe the nature of deficiencies.

Obligations of Holder

¬ Any change or addition in DMF or authorization related to specific customers should be submitted in duplicate copy and with reference to the previous submission.

¬ The reference should include the date, volume, section and / page number affected.

¬ A DMF should contain a list of persons authorized to incorporate the information in the DMF by reference (21 CFR 314.420).

¬ The DMF holder should update the list in the annual update. It should contain the holder's name, DMF number and date of the update.

¬ If any person's authorization is withdrawn during the previous year, it should be identified under a suitable & different caption.[9]

Closure of a DMF

To close a DMF, the holder must submit a request to the DMF staff and indicate that the holder has fulfilled all of his or her obligations.

When a DMF holder fails to update the references and changes in the annual update report promptly from previous updates, the agency may close the DMF.

Reactivating a Closed DMF

Upon submitting a reactivation request, the holder is required to submit a complete copy of the DMF, including any revisions since the last submission. Once the request has been entered into DARRTS, the status of the DMF becomes "ACTIVE".

DARRTS: Document archiving reporting and regulatory tracking, it is an archival system of record for all new and subsequent INDs, NDAs, DMFs, BLAs, ANDA's.[10]

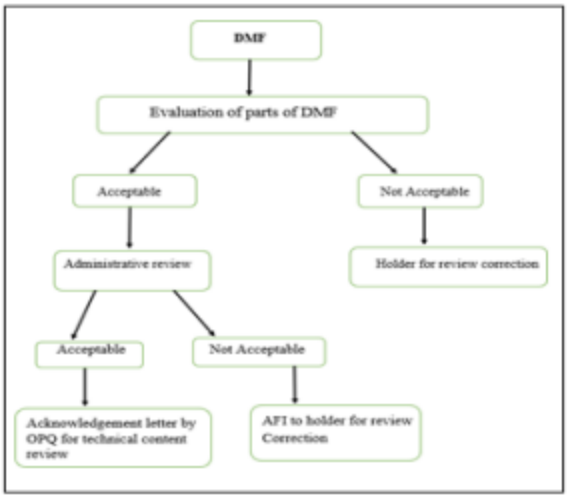


Fig1:Mechanim of drug master file

ASMF Filing Procedure

ASMF includes two parts

1. Applicant's Part: The document is open and contains the information that is said to be non-confidential to the applicant. It should contain adequate information so that the applicant can take full responsibility for the evaluation of suitability for the active substance which is used in the manufacturing of a specified medicinal product. Applicant part still can be considered confidential because it cannot be submitted by anyone to the third parties without the written consent of the EDMF holder.

2. Restricted Part: It is closed, contains all the information which is considered confidential, and all the information such as detailed information about individual stepsof manufacturing methods like reaction conditions, temperature, validation data of critical steps, where the EDMF is provided in CTD format, both summaries should be provided in Quality overall summary type. Both applicants and restricted parts should have version no. and the structure of version no. should be unique and follow a logical order.

Contents of the ASMF

The EDMF should contain all the details related to scientific information for market authorizations for medicinal products in the member states of the European Union.

EDMF, linked to human medicinal products should be present in CTD format, and EDMF linked to the veterinary medicinal products should include.

¬ Name and site of active substance manufacturer

¬ Nomenclature

¬ Description

¬ Outline of the manufacturing route

¬ A detailed description of the manufacturing method

¬ Quality control during manufacture

¬ Development chemistry

¬ Analytical validation

¬ Impurities

¬ Batch analysis

¬ Stability studies

European DMF Filing Procedure

The active substance manufacturer provides the applicant's part DMF to the applicant whichcontains both the applicant & restricted part & then it becomes part of the market authorization application which is then submitted to the authorities.

The main objective of the ASMF is to maintain confidentiality & to protect the information about the active substance, while at the same front allowing the applicant to take full responsibility for the quality, safety & efficacy of the medicinal product. Then National competent authorities assess the complete information which is necessary to check the suitability of active substances in medicinal products.

The EDMF holder should submit to the applicant

¬ A copy of the latest version of the applicant's part

¬ A copy of the quality overall summary on the latest version of the applicant's part

¬ The letter of access, if it is not submitted before for the product.

¬ EDMF holders need to submit the EDMF to the competent authorities when they submitan MAA (market authorization application) or MAV (market authorization variation).

Updates and Changes to ASMF

The holders of EDMFs of all medicinal products should keep the content of their EDMFs updated in light of actual synthesis or manufacturing procedures.

A change to the EDMF should only be made with the written consent of the applicant and competent authority.

Before making any change in EDMF, EMEA and the applicant should be informed. All the changes should be mentioned in a cover letter.

The cover letter to the EMEA should contain the following info.

¬ A summary of all the changes carried out since 1st submission of the EDMF

¬ A comparison between old and new contents of EDMF

¬ Information regarding, whether the change has been accepted, rejected, or with drawn by other member states.

¬ An updated quality overall summary

¬ The new applicant's part / restricted part with each a new version number.

TAB2:Comparative Study of DMF's in USA & Europe

S.no	Requirements	US FDA	EUROPE
1	Regulatory Authority	Food and Drug Administration(FDA)	European Medicine Agency (EMA)
2	Use of DMF in Supportof Application	IND, NDA, ANDA	MAA
3	Mandatory	No	No
4	Provide Information	Drug Substance Intermediate, Drug Products, FlavoursEtc.	Active Substance
5	Fees for Assessment	ANDA Case Only	No Fee
6	Submission in CTDFormat	Required	Required
7	Forms for DMF Filling	Not Applicable Except Type Ii DMF, Form FDA3794	Not Applicable
8	Language	English	English
9	Electronic Submission	eCTD	eCTD
10	DMF Number Assigned by Reviewers	yes	No
11	Approved/Disapproved by Regulatory Authority	Not Approved Only Accepted InSupport Of Applications	Only Accepted
12	Deficiency Letter	Applicable	Applicable
13	Changes and Approved	Applicable	Applicable
14	Appointment of In Country Care Taker	Applicable	Applicable
15	Letter of Authorization	Applicable	Applicable
16	Closure or Withdrawal	Applicable	Applicable
17	Reactivation	Applicable	Applicable
18	DMF FEES	Only for Type 2, DMF fees will be taken according to GDUFA- $31,460	New Applications- £5006

PARA IV FILING & 180 DAY's MARKETTING EXCLUSIVITY FOR FIRST SUCCESSFUL ANDA FILER

(Para Iv Anda Filing = Challenging Weak Patent)

• The Drug Price Competition and Patent Term Restoration Act (Hatch Waxman act) of 1984 streamlined generic drug approval process in US. HWA created an abbreviated process for generic drug approval without conducting costly and duplicative clinical trials. (Under the new legislation, generic entrants need to establish the bio equivalence of its drugs to the original).

• The rules created processes and incentives for both branded and generic companies involving challenges to patents.

• An important section of Hatch-Waxman Act actually encourages generic companies to challenge weak patents.

• If a generic company is the first to file its Abbreviated New Drug Application (ANDA) with a Paragraph IV certification and prevails in the subsequent lawsuit, that generic company is granted a period of market exclusivity of 180 days.

• So, it can price its product slightly below the branded version for six months, take market share from the branded product, and maintain its price point before other generics enter the market and erode the price and segment margins.

• The 180-day exclusivity incentive can be significant for a generic company as it would be the only generic version on the market.

PARA – IV Filing & 180 days exclusivity

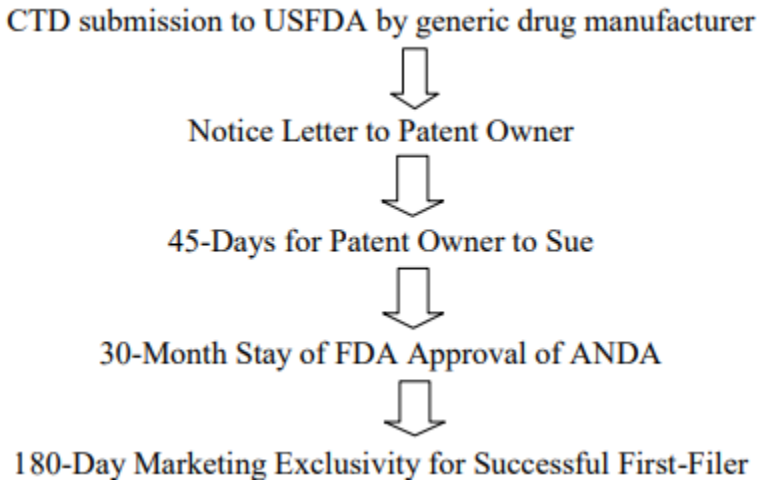
• By making a Paragraph IV filing, the generic drug maker says the patent is at least one of the following:

(1) Invalid

(2) Not infringed

(3) Unenforceable.

Basic Structure of PARA –IV Filing



INFORMATION ACCOMPANYING AN EDMF

The ASM should give permission to the competent authorities to assess the data in the DMF on behalf of a specified applicant in the form of a „Letter of accesses.

Such a letter should include the following information:

- Name and address of the applicant
- Name of product and, if possible, date of application
- Name and address of the ASM
- Name and address of the importer of the active substance, where applicable
- Name and address of the distributor (agent or broker), where applicable.

A written assurance that is a formal agreement between the ASM and the applicant which ensures that if there is a significant change in the manufacturing method (likely to alter the quality or safety of the product) or in active substance specification, this information will be communicated to the applicant and to the authorities. It is the responsibility of the applicant to consider any necessary changes in his specification and to inform the competent

authorities accordingly. A letter of accesses must be lodged by the ASM for every application for marketing authorization.

Critical appraisal of documentation of the edmf

The applicant for the product marketing authorization has the full responsibility for the inclusion in the expert report of the required critical evaluation of the dossier. However, as information in the ASM restricted part of the DMF is not available to the applicant, a critical appraisal should be included in the ASM substance. In particular this section should consider: The manufacturing method and discuss how it will consistently guarantee material of the desired quality;

Batch analysis and whether these show consistency of manufacture;

Demonstration of how the specification and routine tests in the applicant‟s part are justified in relation to the ASM restricted part.

Use of the european drug master file (edmf) procedure

The possibility of submitting confidential data to the competent authorities directly from an Active Substance Manufacturer (ASM), who is different from the applicant for the marketing authorization, is provided for in Directives 75/318/EEC as amended and 81/852/EEC as mentioned.

If there is no problem of confidentiality between the ASM and the applicant for marketing authorization or if the ASM and the applicant can come to an agreement safeguarding confidentiality, all of the information on the active substance should be given directly in the application for the marketing authorization.

Submission of EDMF

An EDMF may be submitted if it is referred in a marketing application for a medicinal product. It should be submitted shortly after the submission of the application, so that the reference number given by the competent authority to the application for marketing authorization can be given in the letter of access. The EDMF may be submitted at the same time as the application, provided an unambiguous reference to the application can be given.

Only ASMs and their authorized representatives (e.g importers) may submit an EDMF. If an applicant for a marketing authorization wants to rely on alternative suppliers of the active substance, he should refer to this situation in the application.

- One copy of the complete EDMF, comprising the 2 parts (applicant‟s part and ASM‟s restricted part) should be sent by the ASM directly to each of the competent authorities concerned.

- A copy of the applicant‟s part should be supplied in advance by the ASM to the applicant. This applicant‟s part should be included in the application for marketing authorization.

- Specific quality requirements for certain dosage forms may be included in the application for marketing authorization. Such requirements will not form part of the EDMF. They should be described in a formal contract between the ASM and the applicant and included in the application for marketing authorization.

- If an EDMF has been updated since the previous assessment, the changes should be clearly identified (particularly those in the method of manufacture and in the specifications of the active substance). If a DMF was not presented in accordance with the current guideline on EDMF‟s (prior to 1992 for human medicinal products and prior to May 1993 for veterinary medicinal products), it should be re-arranged into the 2-part format, and the different parts sent to the authorities.

The specification of the active substance should be identical in the application and in the applicant‟s part of the EDMF. Any proposal from the applicant to use a different test procedure for the purity tests must be fully validated in relation to the procedure used by theactive substance manufacturer, in particular as regards the precision and accuracy of the results of the tests, including the limits of detection for all impurities.

Case Study: USFDA issues warning letters to Ranbaxy Laboratories and an Import Alert for Drugs from two Ranbaxy plants in India citing manufacturing deficiencies. In September 2008, the USFDA issued warning

letters to Indian manufacturer Ranbaxy as it was concerned about deviations from U.S. current Good Manufacturing Practice (cGMP). The Import Alert allows U.S. officials to detain any API and finished drug products manufactured at these facilities (over 30 different generic drugs) at the U.S. border. In addition, until Ranbaxy resolved the noted deficiencies and came into compliance with U.S. cGMP requirements, the USFDA recommended denial for any NDAs and ANDAs that list the cited Ranbaxy plants.23

Case Study: Baxter recalls heparin. In January and February 2008, Baxter, a US pharmaceutical firm which manufactures approximately 50% of the US heparin products, voluntarily recalled its heparin due to nearly 350 reported adverse events, including 19 deaths. Upon the initial recall, Baxter and the USFDA revealed that the recalled heparin products contained a contaminated API. The tainted API, imported from Changzhou SPL China, contained a heparin-like contaminant that was structurally similar to heparin and not recognized in the solution until the FDA developed special testing for it. In March 2008, the FDA announced that they had identified the contaminant to be an altered form of an oversulfated chondroitin sulfate which is not a natural byproduct of the heparin manufacturing process.24 In April 2008, the US government held hearings25 and determined the cause to be non-sterile equipment, lack of following proper procedures, and lack of expertise.

To have an API appear in a drug marketed in Europe, API manufactures need to submit an EDMF (European Drug Master File). API manufacturers also pursue DMFs as the market views them as a sign of quality and they can boost global sales. Figure 327, below shows DMF submissions by Indian and Chinese API manufacturers in recent years and illustrates the recent and stark boom in Indian API manufacture.

CONCLUSION

The DMF contains factual and complete information on a drug product's chemistry, manufacture, stability, purity, impurity profile, Packaging and the cGMP status of any Drug product for humans. The content and the format for Drug Master File is used to obtain marketing Authorization. The main objective of the DMF is to support regulatory requirements of a medicinal product to prove its quality, safety and efficacy. This helps to obtain a marketing authorization grant. Now from 2016 onwards most of the regulated countries will use eCTD or their electronic format for their DMF submission.

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