An Introduction to the API Drug Master File [DMF]

Mahesh Sundar

What is the DMF?

By Definition:

The DMF is a document that provides the regulatory authority with confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs

In short, a DMF is nothing but a very comprehensive and detailed **"PRODUCT BROCHURE",** that provides information on:

- **Who** made the API / Product
- **Where** it was made
- **How** its was made (ie. the mfg process)
- **What** the product contains (viz. Detailed specifications, impurities, self life etc) & details about the quality and storage conditions
- It also provides details with regards to the analysis methods used to qualify the product and other information related to its quality and specs

The DMF can contain confidential and 'IP' related information, & the concept of a DMF allows the mfr to protect such IP related information while sharing them

What is the DMF?

The US FDA states that: *the 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.*

Facts regarding DMFs:

- The submission of a DMF is **NOT REQUIRED BY LAW** or FDA regulation
- A DMF is submitted solely at the discretion of the holder
- A DMF is never approved or disapproved.
    - The technical contents of a DMF are reviewed only in connection with the review of an IND, NDA, ANDA, or an Export Application.

Why then is the DMF required? .....

Why then do you need a DMF ?

• A Drug Product contains a combination of several ingredients, viz., the active, excipients, binders, diluents etc.
• In addition to the Drug Product itself, the IND, NDA or the ANDA has to provide sufficient information to the FDA about the active & inactive ingredients.
• This allows the FDA to effectively review the quality, efficacy and safety of the Drug Product and thereby approve the same

• *The DMF supports the IND, NDA or the ANDA by providing such information on the active or inactive ingredients etc.*

Since most of the ingredients contained in a Drug Product are sourced from different vendors; allows the vendor/party other than the holder of the DMF to **reference material without disclosing to that party the contents of the file.**

In doing this, **DMF serves to complement the Drug Product Dossier** & serves to provide complete information about the product & all ingredients for an effective review by the FDA

Why then do you need a DMF ?....

Protecting Confidential Contents in a DMF

The DMF data compliments the complete Formulations dossier, & provides info on the API or the excipients etc

To protect confidential contents, the FDA allows the DMF to be submitted in 2 parts: The Open part, & the Closed Part (Confidential Data)

Open Part / Applicant's Part:
Non-Confidential info from DMF Filed passed on directly to the Mfr, for submission along with ANDA

Closed Part / Restricted Part:
Contains Confidential info, trade or IP secrets etc.

•This part is usually passed on directly to FDA, for reference along with ANDA filed by the Mfr
•Allows the DMF Holder to avoid confidential data disclosure, while submitting crucial product data to the FDA

The DMF – Open & Closed Parts

The DMF usually has “open” & “closed” parts:

Open Part / Applicant Part:

• Contains information that are not confidential and can be shared with the Drug Product Manufacurer

• The Open part is usually given to the Formulations manufacturer to help understand the API, its characteristics etc and help in development of the Drug Product & the dossier

Closed Part / Restricted Part:

• All confidential data, trade secrets, critical process parameters & IP related data are avoided in the applicant’s part and included in the closed part

• The Closed part is never shared with the Drug Product Mfr, but is directly sent to the Regulatory Authority

Why then do you need a DMF ?

The DMF is usually filed by the supplier of the Active / Inactive Pharma Ingredients and serves to provide info on the Ingredients supplied to the FDA; while maintaining Confidentiality of the data....

Drug Formulation Product Mfr

Drug Formulation Product Mfr intends to file an "ANDA" with the FDA

FDA needs complete info on Active & Inactive Ingredients; to review ANDA

Non-Confidential info from DMF Filed passed on directly to the Mfr, for submission along with ANDA

Confidential info from DMF Filed passed on directly to FDA, for reference along with ANDA filed by the Mfr

Since Ingredients are supplied by a vendor, the Mfr requests for info to the vendor

DMF FILING

....the vendor uses the provision by the FDA to "FILE A DMF" thereby providing confidential data, without really compromising on its mfg secrets!!

Bulk Drug / Excipient Vendor

The information consists of various data that is confidential trade / manufacturing details that cannot be shared...but since FDA needs to be given such data.....

Types of DMFs

The US FDA classifies information filed as DMFs under 5 categories:

Type I –

Manufacturing Site, Facilities, Operating Procedures, and Personnel
(no longer applicable & has been discontinued since 2000)

Type II –

Drug Substance (APIs), Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product

Type III –

Packaging Material

Type IV –

Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation

Type V –

FDA Accepted Reference Information

Contents in a DMF

• The Structure of a **Regulatory 'Marketing Application' Dossier** was harmonised by the EMA, Europe, US FDA & the Ministry of Health, Labour and Welfare (Japan).

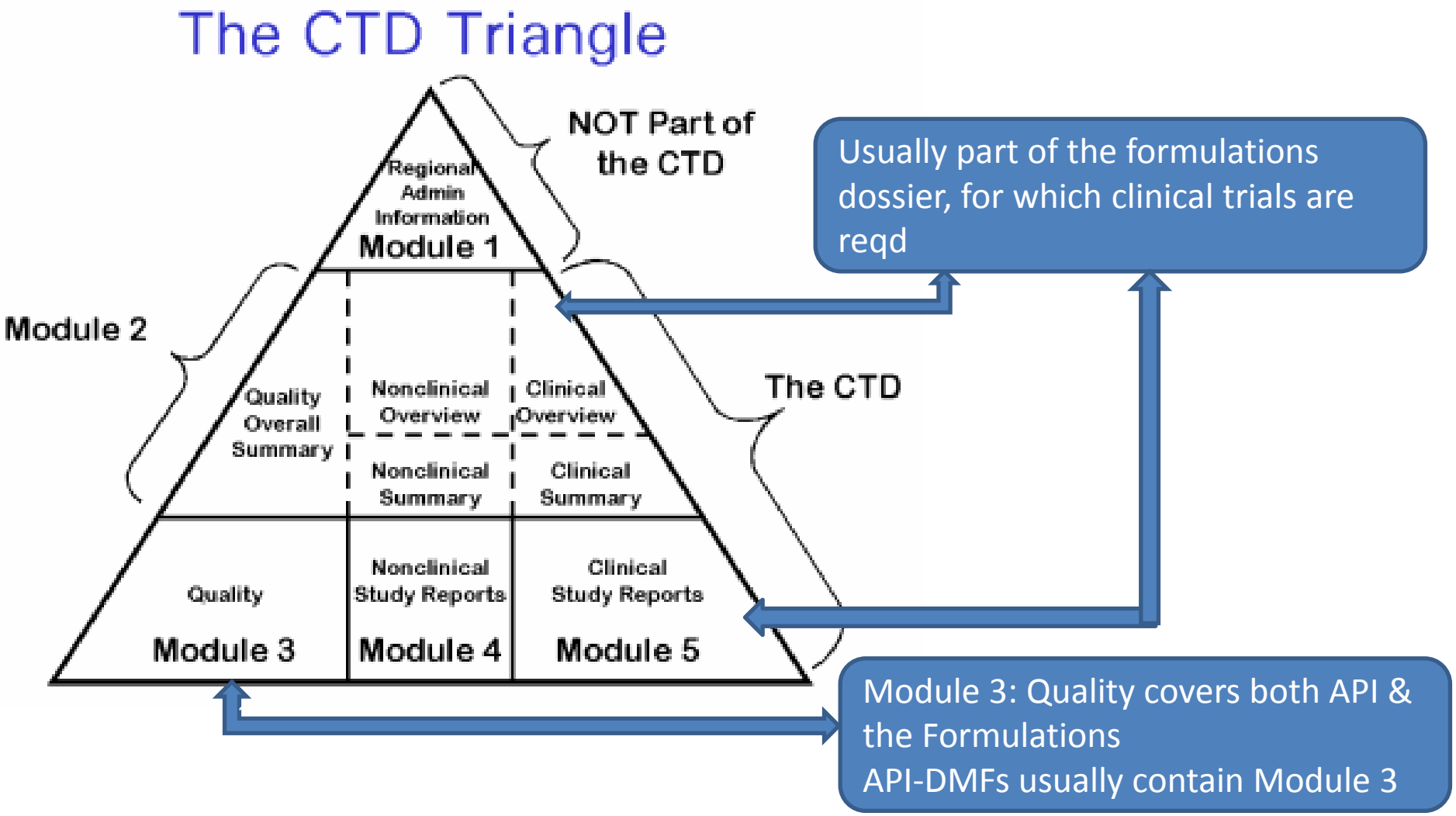
• A common structure was jointly agreed upon by the above major drug controlling bodies and was put-into force

• The result was the development of the **"Common Technical Document"**, which is to be used for Regulatory Submissions ;

• & accepted almost all over the world

The Common Technical Document has a **pre-set format** which the applicant has to follow while drafting a submission document

The ‘CTD’ Format



DMF – CTD Structure

As in the CTD Triangle, the dossier consists of **5 Modules**

Module 1:
Regional Administrative Info – tends to vary from region but always included in complete CTD structure

Module 2:
Contains all summaries & product overviews (QOS etc.)

Module 3:
Contains Info on the Quality of the Drug Substance / Product

Module 4:
Preclinical Study Parameters

Module 5:
Clinical Study Data

CTD Module 1: Administrative Information in the DMF

The Module 1 is not covered by the “CTD” & varies in every region

For the US-DMF submissions, this module usually contains:

- Cover letter, Commitment Letters
- Contact Information of the DMF Holder, mfg site address & details, US Agent contact details
- Letter of Authorisation (or the ‘LOA’)
- Other / Miscellaneous Information

CTD Module 2: All Summaries & Overviews

Section-wise Content

- 2.1 Overall CTD
- 2.2 CTD Introduction
- 2.3 Quality Overall Summary
- 2.4 Non-Clinical Overview
- 2.5 Clinical Overview
- 2.6 Non-Clinical Written and Tabulated Summaries
- 2.7 Clinical Summary

CTD Module 2: QOS Formats to be Used

- 2.3 Introduction
- 2.3.S Drug Substance
- 2.3.P Drug Product
- 2.3.A Appendices
- 2.3.R Regional Information

CTD Module 3: Structure & Contents for the Drug Substance

- 3.2.S DRUG SUBSTANCE
- 3.2.S.1 General Information
- 3.2.S.2 Manufacture
- 3.2.S.3 Characterization
- 3.2.S.4 Control of Drug Substance
- 3.2.S.5 Reference Standards or Materials
- 3.2.S.6 Container Closure System
- 3.2.S.7 Stability

CTD Module 3: The Details

S1 General Information

- 1.1 Nomenclature
- 1.2Structure
- 1.3 General Properties

S2 Manufacture

- 2.1 Manufacturer (s)

S3 Characterisation

- 3.1 Elucidation of Structure and other Characteristics
- 3.2 Impurities

S4 Control of Drug Substance

- 4.1 Specification
- 4.2 Analytical Procedures
- 4.3 Validation of Analytical Procedures
- 4.4 Batch Analysis
- 4.5 Justification of Specification

S5 Reference Standards or Materials

S6 Container Closure System

S7 Stability

CTD Module 3: Structure & Contents for the Drug Product

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

3.2.P.2 Pharmaceutical Development

3.2.P.3 Manufacture

3.2.P.4 Control of Excipients

3.2.P.5 Control of Drug Product

3.2.P.6 Reference Standards or Materials

3.2.P.7 Container Closure System

3.2.P.8 Stability

Table 1	NtA CTD format	Applicants Part	Restricted Part
3.2.S.1	General information	x	
3.2.S.1.1	Nomenclature	x	
3.2.S.1.2	Structure	x	
3.2.S.1.3	General properties	x	
3.2.S.2	Manufacture	x	X
3.2.S.2.1	Manufacturer(s)	x	
3.2.S.2.2	Description of Manufacturing Process and Process controls	1)	2)
3.2.S.2.3	Control of Materials		X
3.2.S.2.4	Control of critical steps and intermediates	3)	4)
3.2.S.2.5	Process validation and/or Evaluation		X
3.2.S.2.6	Manufacturing Process Development		X
3.2.S.3	Characterisation	x	
3.2.S.3.1	Elucidation of Structure and other Characteristics	x	
3.2.S.3.2	Impurities	x	5)
3.2.S.4	Control of Drug Substance	x	
3.2.S.4.1	Specification	x	
3.2.S.4.2	Analytical procedures	x	
3.2.S.4.3	Validation of analytical procedures	x	
3.2.S.4.4	Batch analysis	x	
3.2.S.4.5	Justification of specification	x	6)
3.2.S.5	Reference standards or materials	x	
3.2.S.6	Container Closure System	x	
3.2.S.7	Stability	x	
3.2.S.7.1	Stability summary and conclusion	x	
3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment	x	
3.2.S.7.3	Stability data	x	

Inclusions in the Open & Closed Part DMFs as suggested by the EMA for EDMFs

The DMF - Notes

- The DMF is almost always reviewed in connection with a formulations' marketing application (an ANDA or an NDA etc.)
- Though the DMF is never approved, its successful review allows the marketing application to be finally approved
- The US FDA however, allows the holder to file a DMF, even if there are no ANDAs referring to the DMF, at the time of filing. The FDA allows the holder to file and list the DMF in their website. A DMF No is allotted

- As per recent GDUFA guidelines in the US, fees need to be paid by the DMF holder to review the DMF

- The EU provides a CEP certification for DMFs that comply to the European Pharmacopeia

The DMF - Notes

- The USFDA lists DMFs starting from the year 1940 though the number of filings have picked up from the late 1980s

- The US FDA has several thousands of DMFs filed out which India ranks No#1 with most numbers of filed DMFs (~2500 DMF filings as of 2011)

Thank you, Folks!