DRUG MASTER FILES

CYCLONE PHARMACEUTICALS

CONTENTS:-

I. Introduction

DRUG MASTER FILES

A Drug Master File (DMF) is a submission to the FDA of information, usually concerning the confidential detailed information about Chemistry, Manufacturing and Controls (CMC) of a drug product or a component of a drug Product.

Other non CMC – information (like packaging, storing) may also be filed in a DMF.

TYPES OF DMFS

Originally Five Types…

I Plant information

II Drug substance, drug product, intermediates and material used in their manufacturing.

III Packaging

IV Excipients.

V Other information which is generally not covered by type I to type IV drug master files.
(Usually clinical, toxicity data are covered.)

CURRENT TYPES OF DMFS

Now Four Types:

TYPE I DMF WITHDRAWN.

(Numbering retained to avoid confusion)

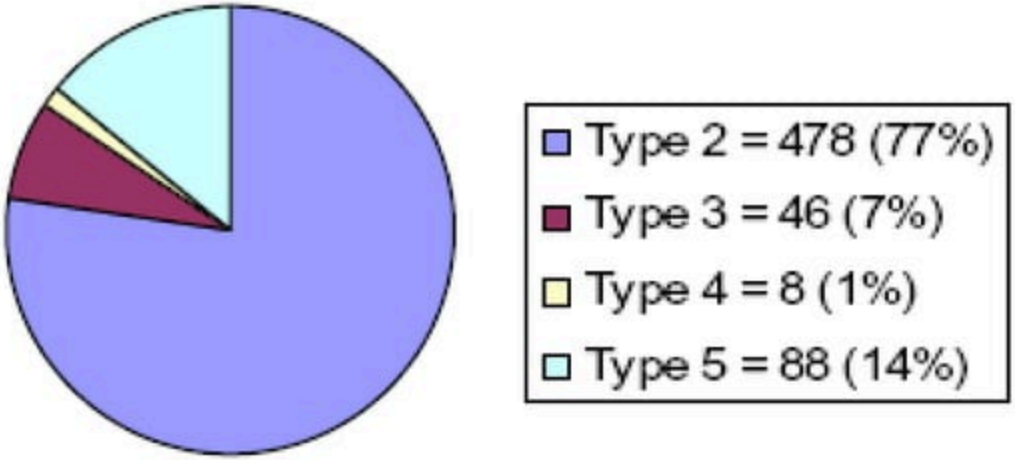
II Drug substance, drug product, intermediates and material used in their manufacturing.

III Packaging

IV Excipients

V Other information which is generally not coverd by type I to type IV drug master files.

RATE OF DMF FILING AS OF MARCH 2007



WHO MUST FILE A DMF?

NOBODY

There is no legal or regulatory requirement to file a DMF. A DMF may be filed to provide CMC information that the FDA reviews.

The information contained in DMF may be used **to support** an IND / NDA /ANDA ,another DMF,an export application or amendments and supplements of any of these.

Remember that,
DMF is **NOT a substitute** for IND / NDA / ANDA or export application.
Technical contents of a DMF are reviewed only in connection with the review of IND /NDA /ANDA or an export application.

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II. SOME BASIC TERMINOLOGIES

HOLDER: The person /company **who submits** DMF.

AGENT : The person / company **who represents** a DMF HOLDER.
(*Also called Representative*.)

APPLICANT / CUSTOMER / AUTHORISED PARTY (AP) :The person / company **who references** the DMF.

APPLICATION:Investigational New Drug Application (IND), New Drug Application (NDA), Abbreviated New Drug Application (ANDA)

SUPPLEMENT TO AN ANDA / NDA: **A report of change** in an **approved** ANDA / NDA.

AMENDMENT TO AN APPLICATION: **Additional information to**…

an existing IND,
a pending ANDA / NDA
a pending ANDA / NDA supplement.

III. TYPES OF DMFS WITH THEIR CONTENTS

Type I : plant information

Points included:

Manufacturing site
Equipment capabilities
Operational layout
Actual site address
A map showing its location with respect to the nearest city
Corporate headquarters

As per Jan. 12, 2000 FR notice : Elimination of Type I DMFs done by July 10, 2000.

YPE II DMF

CONTENTS:

(1)Drug Substance Intermediates, Drug Substances, and Material Used in Their Preparation.

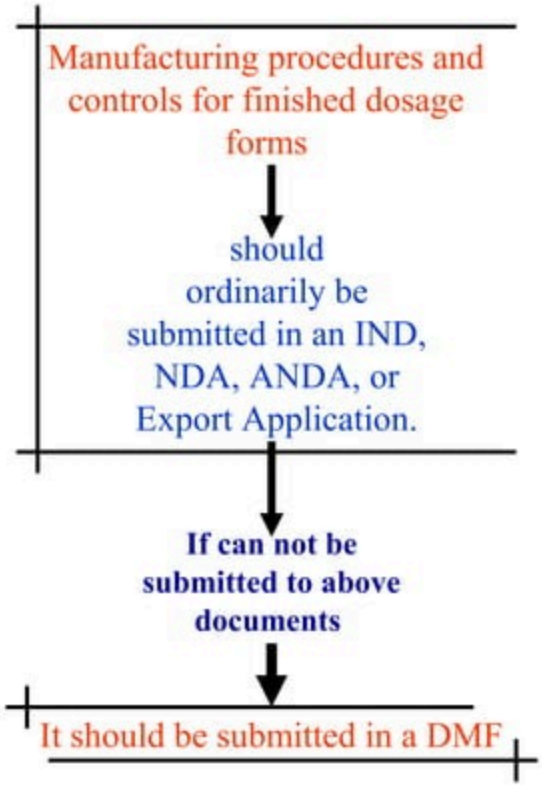
It Summarizes all significant steps in the manufacturing and controls of the drug intermediate or substance.

Detailed guidance on what should be included in a Type II DMF for drug substances and intermediates may be found in the following guidelines:

1.Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances.

2.Guideline for the Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application.

(2) Drug Product (finished dosage forms)



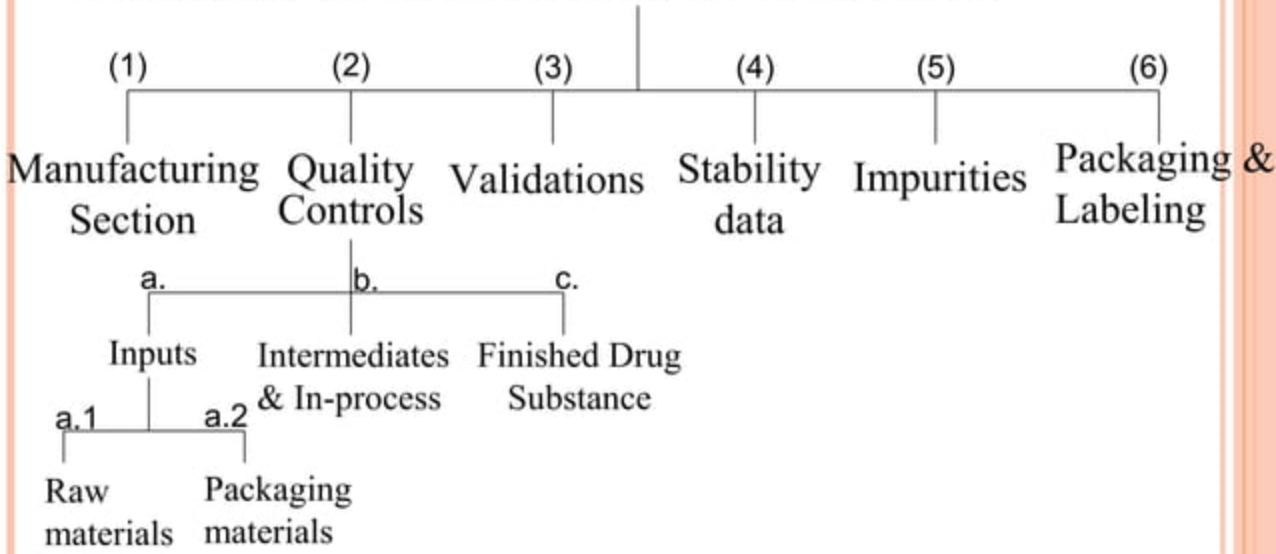
For a drug product, the applicant/sponsor should follow the guidance provided in the following guidelines:

1.Guideline for the Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application.

2.Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products.

3.Guideline for Submitting Samples and Analytical Data for Methods Validation.

GENERAL POINTS INCLUDED IN TYPE II DMF



YPE III: PACKAGING MATERIAL

Contents:-

- ✓ Packaging material intended for which use.
- ✓ Its components and composition.
- ✓ Names of the suppliers or fabricators of the components used in preparing the packaging material.
- ✓ Acceptance specifications.
- ✓ Toxicological data on these materials.

- ✓ FOLLOW THE GUIDELINE: "*Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics*."

BUT REMEMBER THAT,

Responsibility for compatibility and safety of packaging components in finished drug product is the responsibility of the AUTHORISED PARTY(AP).

It is not the responsibility of DMF HOLDER.

EXCIPIENTS

- CMC for a compendial excipient is usually not reviewed and therefore a DMF is not necessary.

- Exceptions: New route of administration or total dosing that may affect safety and efficacy. E.G..RESPITOSE, lactose for dry powder inhalation products.

- CMC requirements for a novel excipient should be submitted same as type II DMF.

TYPE V DMF

FDA discourages the use of Type V DMFs for miscellaneous information, duplicate information, or information that should be included in one of the other types of DMFs.

TO SUBMIT THE DATA WHICH IS NOT COVERED IN TYPE I TO IV DMF

(CLINICAL / TOXICITY DATA)

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A holder must first submit a letter of intent to the drug master file staff

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FDA will then contact the holder to discuss the proposed submission.

IV. SUBMISSIONS OF DRUG MASTER FILES

How the System Works ?

- Holder sends the DMF (NO FEE two copies) to

- Containing:
  - 1 – Transmittal (cover) letter
  - 2 – Administrative information
  - 3 – Technical information

✓ Follow the Guideline at www.fda.gov/cder/guidance/dmf.htm

✓ Binders recommended http://www.fda.gov/cder/ddms/binders.htm

1 – TRANSMITTAL (COVER) LETTER

Original Submissions and Amendments

- Identification of submission.
  (Original /supportive to original DMF / Amendment)
- Type of DMF and subject (update, revised formula, or revised process)
- The name and address of each sponsor, applicant, or holder, and all relevant document numbers.
- Signature of the holder or the authorized representative.
- Typewritten name and title of the signer

ADMINISTRATIVE INFORMATION

Original Submissions:

a. Names and addresses of the following:
(1) DMF holder.
(2) Corporate headquarters.
(3) Manufacturing/processing facility.
(4) Contact for FDA correspondence.
(5) Agent(s), if any.

b. The specific responsibilities of each person listed in any of the categories in Section a.

c. 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 – ADMINISTRATIVE INFORMATION

Amendments

a. Name of DMF holder.

b. DMF number.

c. Name and address for correspondence.

d. Affected section and/or page numbers of the DMF.

e. The name and address of each person whose IND, NDA, ANDA, DMF, or Export Application relies on the subject of the amendment for support.

f. The number of each IND, NDA, ANDA, DMF, and Export Application that relies on the subject of the amendment for support, if known.

g. Particular items within the IND, NDA, ANDA, DMF, and Export Application that are affected, if known.

DMF reviewed for administrative purposes ONLY by Central Document Room (CDR) staff.

DMF entered into **DMF DATABASE**, assigned a number, and a letter sent to the HOLDER.

If no response from FDA side,…

DMF HOLDER can put a query on the e-mail: dmfquestion@cder.fda.gov

Letter sent by FDA to DMF HOLDER consists of …

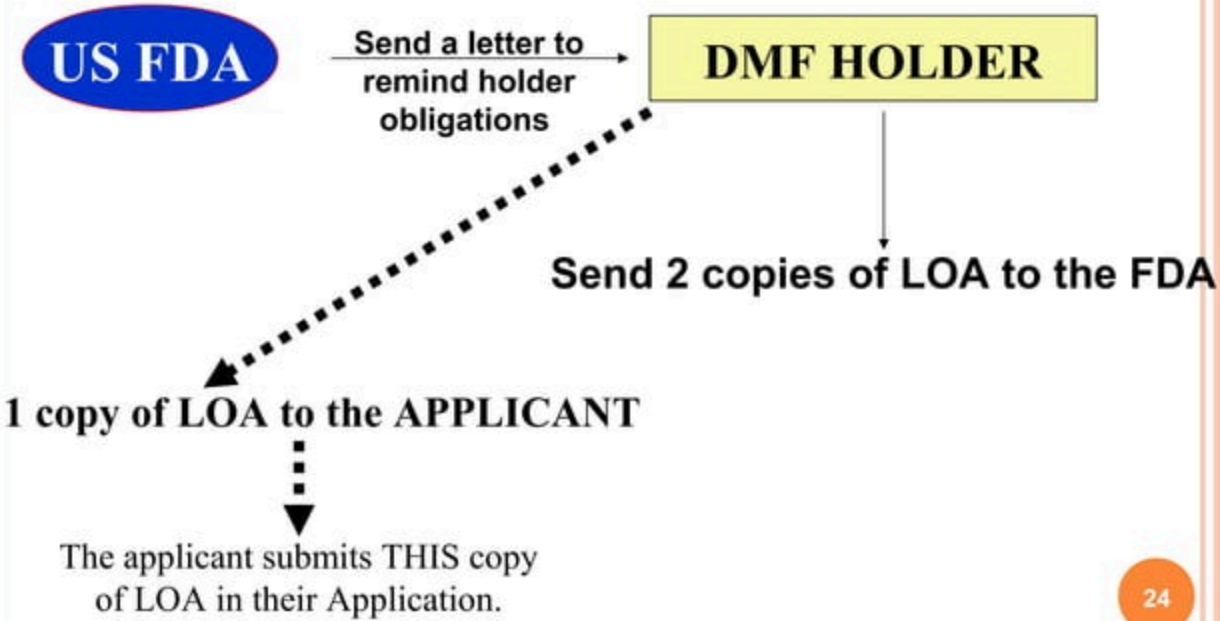
- Number given to DMF in database and Type.

- Reminder of obligations (responsibilities) of holder :

– Submit all changes as amendments.
– Notify FDA of change in holder name or address.
– Notify FDA of change in agent/representative.
– SUBMIT ANNUAL UPDATE (Annual Report).
– Submit Letter of Authorization (LOA) for each item referenced.

LETTER OF AUTHORIZATION (LOA)

The DMF will be reviewed ONLY when it is referenced in an Application or another DMF.



IMPORTANCE OF LOA

- Sending LOA is the only mechanism which triggers the review procedure of DMF.
- A letter of authorization permits the FDA to reference the DMF.
- If the holder cross references its own DMF, the holder should supply following information in a LOA.
  - -DMF number
  - -Specific product(s) covered by the DMF
  - -Section numbers and/or page numbers to be referenced
- In Europe, the permission to reference a DMF is called a Letter of Access.

REVIEW OF THE DMF

REVIEWER

When reviewer receives an application (IND/NDA/ANDA) that references a DMF

Requests the DMF from the CDR (central document room)

but Delivery of DMF can take a couple of days.

This review procedure of DMF is in Contrast with APPLICATION, where document is delivered **automatically to reviewer.**

Next slide

After getting DMF,the Reviewer starts the review procedure

If Reviewer found any deficiency in the content of DMF,

The DETAILED DEFICIENCIES are communicated to the holder.

HOLDER should submit the REQUESTED INFORMATION to the DMF in response to the agency's deficiency letter along with transmittal letter having subject matter.

The APPLICANT is also notified but, the nature of the deficiencies is not communicated to the applicant.

If no deficiencies, no letter, applicant not notified.

Differences between Applications and DMFs

Applications	DMFs
1. COMES UNDER REGULATORY STATUS.MUST BE FILED BY APPLICANT.	1.NOT COME UNDER REGULATORY STATUS.IT IS NOT MANDATORY TO FILE A DMF.
2. EACH APPLICATION AND ITS SUPPLEMENT ARE ENTERED INTO A COMMON DATABASE.	2. DMFs ARE ENTERED IN TO DATABASE AS PER THEIR TYPES. (SEPARATE DATABASE FOR EACH TYPE OF DMF)
3.SUBMITTED TO A PARTICULAR REVIEW DIVISION.	3.SUBMITTED TO CDR.
4. ASSIGNMENT TO A REVIEWER AND EACH SUBMISSION HAS A DUE DATE.	4.NO ASSIGNMENT TO A REVIEWER, NO DUE DATE.
5.REVIEW PROCEDURE QUITE DIFFERENT THAN DMF.	5.DMFs ARE REVIEWED ONLY WHEN REFERENCED BY APPLICATION OR ANOTHER DMF
6.IF THE ANNIVERSARY DATE FOR ANNUAL UPDATE IS MISSED FDA SENDS A REMINDER.	6.IF THE ANNIVERSARY DATE FOR ANNUAL UPDATE IS MISSED FDA WILL NOT SEND A REMINDER.

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ANNUAL UPDATE OF DMF

- The holder should provide an annual report on the anniversary date of the original submission.
- If the subject matter of the DMF is unchanged, the DMF holder should provide a statement that the subject matter of the DMF is current.
- Failure to update can cause delays in FDA review of a pending IND, NDA, ANDA or any amendment or supplement to such application; and FDA can initiate procedures for closure of the DMF.

RETIRING DMFS

If a DMF has no activity (amendment or annual report) in three years FDA will initiate retirement procedure.

Note: LOA is not counted for activity.

DMF RETIREMENT PROCEDURE

- FDA sends overdue notice letter (ONL) to holder and/or agent using most recent address.

- If no response in 90 days, one copy of DMF is sent to Federal Records Center (FRC) and the other is destroyed.

CHANGES IN DMF SYSTEM

- Over the past decade, there have been some changes in the DMF system to help make it work better.
- However some things remain the same.

CHANGES IN THE DMF SYSTEM AND PROCEDURES (INTERNAL)

- Creation of Review Cover Form
- Creation of Type II Review Format
- Implementation of Re-review Policy
- Creation of Central Review File
- Revision of Database View

CHANGES IN THE DMF SYSTEM AND PROCEDURES (EXTERNAL)

- Elimination of Type I DMFs
- Post-Approval Changes Guidance and
- Creation of DMF List Website
- Creation of DMFQUESTION
- Establish Position of DMF Expert

UNCHANGED THINGS OF DMF

- No review of DMFon receipt of it.
- Review only when referenced in application.
- All of the DMF is still confidential.
- DMFs are neither approved nor disapproved.
- The holder still has the responsibility to notify customer of changes.

SUMMARY

- The DMF system presents challenges for both the industry and the FDA.

- Some of the changes have made the system smoother
(hopefully for both industry and FDA).

- Problems can be minimized:

– With full understanding of their responsibilities and adherence to Guidances on the part of holders and applicants.

– With adherence to policies and procedures on the part of reviewers.

THIS WAS ALL ABOUT
WHAT USFDA SAYS
ABOUT DMF.

NOW,...
WHAT EUROPEAN DRUG MASTER FILE PROCEDURE FOR ACTIVE SUBSTANCES SAYS ABOUT THE DMF...

CONTENT OF DRUG MASTER FILE

2 PARTS

APPLICANT'S PART OF DMF → OPEN PART

ASM RESTRICTED PART OF DMF → CLOSED PART

APPLICANT'S PART OF DMF

OPEN PART

(AVAILABLE TO APPLICANT)

ACTIVE SUBSTANCE MANUFACTURER → **SUPPLIES INFORMATION TO THE APPLICANT**

THIS INFORMATION INCLUDES:

- **outline of the manufacturing method**
- **impurities originating from the manufacturing method, isolation procedure and degradation**
- **information on the toxicity of specific impurities**

- The applicant's part of a DMF is provided by the ASM to the applicant directly and becomes part of the application for marketing authorization.

- The applicant's part of the DMF is still a confidential document which cannot be submitted to third parties without the written agreement of the ASM.

ASM RESTRICTED PART OF DMF

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CLOSED PART

(NOT AVAILABLE TO THE APPLICANT)

IT INCLUDES:

Detailed information about…

- ✓ **Individual steps of the manufacturing method such as reaction conditions, temperature,**
- ✓ **Validation and evaluation data for certain critical steps of the manufacturing method,etc.**

Such information is supplied to the authorities only.


Thanks