INSIDE STORY FOR REVIEW OF DMF AND DOSSIERS BY REGULATORY AUTHORITIES

(Part I: ANDA, NDA & DMF)

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This article is solely written by him to guide RA Professionals for regulatory submissions. The article is based on self experience of 25 years of the author

Introduction:

Food and Drug Administration (FDA) grants approval for marketing authorization for new as well as generic drugs against review of detailed scientific, clinical and non clinical information included in the application called as NDA, ANDA and DMF

FDA is very transparent in procedures and policies for the contents and review of theses submissions. This article is written to explain the inside review procedures followed by FDA for the same.

The article will be very useful in designing, drafting, and submission and follow-up of all regulatory submission with FDA.

The article is divided into 3 sections.
1.0 Inside story for review of ANDA (Review of Generic Drug Applications)
2.0 Inside story for review of NDA (Review of New Drug Applications)
3.0 Inside story for review of DMF (Review of information in support to ANDA and NDA)

The article defines information required for review and mechanism for approval/rejection of a particular application.

1.0 INSIDE STORY OF ANDA REVIEW

1.1 Submitting ANDA

Following information in prescribed form is required for submitting ANDA

Information on the product in form 2657
Information on manufacturing facility in form 2656
Information as per FDA forms 356h and form 3674
Cover letter
(You may download these forms from internet)

Information as per 5 MODULE ICH CTD Guidelines (see below)
(This information has to be compiled by your QC/QA and Regulatory Department)

CTD Module 1: Administrative documents
CTD Module 2: Quality, non-clinical and Clinical Overviews and summaries
CTD Module 3: Detailed Quality information on API and Dosage Form
CTD Module 4: Non Clinical Study Reports (as available)
CTD Module 5: Clinical Study Reports (as Full text Papers)

The entire set of information shall be submitted in triplicate as per below:

Archival Copy- The archival copy is a complete copy of the application. It serves as the official archive of the application and may be used during the review of the application. It shall have blue color binder

Review copy- It includes the information needed by each review discipline for its evaluation. It shall have red color

Field copy- It contains only Quality section (Module 3). It shall have Green Color
The information provided in any format other than this may get "Refuse to File" letter from FDA

Paper size-Standard U.S. letter size paper (8.5 x 11 inches) should be used for all submissions.
Font size-Narrative text is submitted in Times New Roman 12 point font. Font sizes 9 to10 points are considered acceptable in tables.
Pagination-Page numbering should be at the document level and not at the volume or module level. (The entire submission should never be numbered consecutively by page.) In general, all documents should have page numbers. Since the page numbering is at the document level, there should only be one set of page numbers for each document

Please Note that the following admin information (as to be included in CTD Module 1 is very critical

- Field copy certification
- Debarment certification
- Financial Certification
- Patent information on any patent that claims the drug, if applicable
- Patent certifications
- Letters of authorization for reference to other applications or drug master files (if applicable)
- US Agent Letter of Authorization
- Proprietary name request (if applicable)
- Basis of ANDA submission
- Comparison between Generic Drug and RLD-505(j) (2) (A)
- Request for waiver
- Draft labeling
- Listed drug labeling
- Labeling requirements
- Financial disclosure information
- Waiver requests
- Environmental assessment or request for categorical exclusion
- Statements of claimed exclusivity and associated certifications
- **Prescribing information (Actual copies to be provided)**
- Container and package labels
- Package inserts
- Draft labeling
- Patient leaflets
- Information sheets
- Medication Guides
- **Labeling comparison with approved product**

1.2 ANDA REVIEW PROCEDURE

Incomplelete and Deficient applications are promptly issued "refuse to file letter" letter
Site verification and inspection concurrent with the application review. If the facility is deficient in GMP Compliance the approval is held up till the deficiencies are rectified.
Admin and technical info (CTD Documentation) is reviewed by OGD/CDER review team If Admin and Technical information (Labeling, Chemistry , Manufacturing, Control and Microbial Safety) info as provided in CTD submission is un-satisfactory "Not approvable "letter is issued to the applicant.
If BE study results are not satisfactory "bio deficiency " letter is issued to the applicant
When there are no queries the applicant finally receives FDA approval letter.

2.0 INSIDE STORY OF NDA REVIEW

Types of NDA which are accepted by FDA	1- New Molecular Entity 2- New Salt of Previously Approved Drug (not a new molecular entity) 3- New Formulation of Previously Approved Drug (not a new salt OR a new molecular entity) 4- New Combination of Two or More Drugs 5- Already Marketed Drug Product - Duplication (i.e., new manufacturer) 6- New Indication (claim) for Already Marketed Drug (includes switch in marketing status from prescription to OTC) 7- Already Marketed Drug Product - No Previously Approved NDA
To whom the application shall be addressed?	Center for Drug Evaluation and Research Food and Drug Administration Document and Records Section 5901-B Ammendale Rd Beltsville, Md. 20705-1266
Which applications are considered on priority?	S- Standard review for drugs similar to currently available drugs. P- Priority review for drugs that represent significant advances over existing treatments
What is the Submission Package?	Filled up Administrative Forms Duly completed 5 Module CTD on the drug product Safety Update Report (typically submitted 120 days after the NDA's submission) Case Report Tabulations and Case Report Forms Patent Information and Patent Certification Any Other Information as required

2.1 How the Application is reviewed?

Technical Review (Module III Review)	Initially Module III is reviewed. If it is incomplelete “refuse-to-file" letter is issued to the applicant and NDA is kept on hold. The time limit for this initial review is 60 days.
Medical/Clinical reviewers	This is performed by a team of Medical reviewers
Biopharmaceutical Review	This is performed by Pharmacokineticists. This is the check for bioavailability, distributed in, metabolized by, and eliminated from the human body.
Statistical Review	This is performed by Bio-Statisticians.
Microbiology Review	Microbiology Review is required only for anti-infective drugs.
Consultation with Advisory Committees	Consultation/advice from advisory committees is generally taken before finalization of Approval.(PN: Committee recommendations are not binding on CDER)
Clarifications from Meetings with	CDER uses telephone , letters, faxes ,face-to-face meeting or videoconferencing to communicate to clarify the technical /admin

Sponsor	issues with sponsors
Preapproval Site Inspection	Before considering final approval , the manufacturing site is inspected for the followings: The accuracy and completeness of the manufacturing-related information and commitments submitted in the NDA; The manufacturing controls for the preapproval batches Current Good Manufacturing Practices (CGMPs) During the inspection FDA officers also collect a variety of drug samples for analysis in CDER laboratories.

2.2 How the Applicant is responded?

Not Approved Letter	This letter provides the list of deficiencies in the application for not approval of the application
Approvable Letter	This letter provides the lists minor deficiencies that can be corrected. It signals that the application can be approved upon meeting the deficiencies.
Approval Letter	This letter confirms the approval

3.0 INSIDE STORY OF US DMF REVIEW

Type of DMFs	Originally Five Types I Plant information (It has been discontinued) II Drug substance, drug product, intermediates and material used in their manufacture III Packaging IV Excipients V FDA Accepted Reference Information (Not much in use)
Type II DMF	Type II (Drug Substance Intermediates, Drug Substances, and Material Used in Their Preparation) Type II DMF is reviewed for significant steps in the manufacturing, Quality Control, Validations, Stability, Impurity Profile and Packaging & Labeling as per module 3 of CTD format.
Type III DMF	It is intend for Packaging material used for Human Drugs and Biological. It is reviewed as per the "Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics" The following points are essentially discussed: Intended use of Packaging material 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 Please note DMF Holder is not required to undertake the responsibility of compatibility and safety of packaging components in finished drug
Type IV	It is intended for Excipients used in Drug Products.

	CMC for compendia excipients is usually not reviewed However, CMC for a novel excipients should be submitted same as type II DMF.
What is the current regulatory status of DMF?	There is no legal or regulatory binding to file a DMF. It is not reviewed on receipt. It is reviewed only when referenced in application such as NDA/ANDA. DMFs are neither approved nor disapproved.
Who's who in DMF Filing?	The person or company who submits a DMF is the HOLDER The person or company who represents a DMF HOLDER is the AGENT The person or company who references the DMF is the APPLICANT
Why DMF are filed?	DMF are filed to Maintain confidentiality of proprietary information (e.g. Manufacturing Formula and manufacturing Technology) of the products for which DMF is filed
What are the major contents of DMF submissions?	Following Documents must accompany every submission of DMF: Transmittal (cover) letter Administrative information of DMF Holder Technical information on the product for which DMF is designed
How DMF Filing System Works?	Documents provided in DMF are checked (not reviewed) for administrative purposes by Central Document Room (CDR) staff. DMF entered into DMF database, assigned a number, and acknowledgement letter sent If no acknowledgment letter in 3 weeks the CDR may be contacted on phone 301-827-4210 or by dmfquestion@cder.fda.gov Each DMF Filing is acknowledged by FDA through a Letter which contains the following information : Assigns number and Type Reminder of obligations of holder
What are the Obligations of DMF Holder?	DMF Holder must : Submit all changes as amendments Notify FDA of change in holder name or address Notify FDA of change in agent/representative Submit annual report on the anniversary date of DMF filing. Issue Letter of Authorization (LOA) to each customer who intends to use the product
When DMF is reviewed?	The DMF will be reviewed ONLY when it is referenced in an application like ANDA or NDA
How the Applicant is confirmed that DMF is under review?	DMF sends one copy of LOA to the APPLICANT LOA must contain a specific reference to a particular item in the DMF
How DMF is triggered?	The DMF is triggered (taken for review) when the applicant submits LOA in their NDA/ANDA/IND
How FDA helps in Filing DMF?	The DMF holder can ask for any guidance/help by email addressed at : dmfquestion@cder.fda.gov
How can you check your status of DMF	The status of DMF whether it is active or withdrawn can be checked on FDA website.

Filing?	
Does the agent is required for DMF Filing?	Normally Agent is not required for DMF Filing. However, he is recommended to facilitate communication
Who Appoints Agent?	The agent is appointed by DMF Holder to file DMF and to communicate with FDA. However, DMF can also be filed directly
What precautions shall be taken while Drafting Appointment Letter of an Agent?	Do not use the word "authorize" or "authorization". Always that particular person was appointed
What are the current Amendments in DMF Review procedures?	The DMF is reviewed only when referenced in NDA/ANDA. Currently FDA has 1. Review Type II DMF has been defined by FDA 2 FDA has Made provisions for re-review of DMF if required. 3.FDA has created Central Review File 4. FDA has issued Post-Approval Changes Guidance (BACPAC) 5. FDA has eliminated AADAs for bulk antibiotics 6.FDA has defined need for Expert Review
Who must file DMF?	DMF filing is not mandatory. However, A person manufacturing Novel Excipients must file DMF
What symbols are used for indicating the status of DMF	"A" = Active. This means that the DMF was found acceptable for filing, administratively, and is up-to-date. "I" = Inactive "N" = Not an assigned number "P" = DMF Pending Filing Review
Which DMF are never reviewed?	DMF for OTC Products and Compendia excipients are never reviewed.
Who and when LOA is submitted?	DMF Holder shall submit Two copies of LOA to FDA and one copy to the ANDA/NDA Applicant. LOA may be submitted along with DMF Filing or it may be submitted later on at any time.
What precautions shall be taken while Drafting LOA?	Do not use the word appoint for appointment? Always use "authorize" or "authorization"
When DMF No is assigned?	It is assigned only when FDA receives 2 Copies of DMF along with transmittal and admin letters. It can not be assigned in advance
How DMF is registered	DMF is submitted to CDR. It is simply entered into DMF database.
How Deficiencies in DMF are communicated?	DMF are not reviewed until it is triggered. However, if any deficiencies are noted during the review, the same are communicated to the holder and the applicant is simply notified.
How much time is required for the Registration of DMF on receipt by FDA?	Once DMF is received at CDER it is forwarded to Central Documentation Room and is registered immediately. Delivery of DMF can take a couple of days. Reviewers are in four different buildings all over Rockville.
What are the Administrative provisions for DMF?	FDA allows Change in holder name and/or his address Holder can appoint an Agent and can also terminate the appointment without giving any reasons. Holder can voluntarily Request closure of DMF

	Holder can issue new LOA to the applicant when his name and address is changed.
Does each of minor change is required reporting?	No. Each minor technical change is not required for reporting. However, any change in Admin information shall be reported promptly. If a change is "Annual Reportable", report in AR or amendment to DMF and notify customer that AR changes have been made.
What happens when DMF has no activity?	When there is no communication from DMF holder for 3 consecutive years (i.e. no annual report) FDA initiate retirement procedure.
What Administrative information is required for Original DMF Submission?	For original application following information shall be provided to FDA 1.Names and addresses of the : (1) DMF holder. (2) Corporate headquarters. (3) Manufacturing/processing facility. (4) Contact for FDA correspondence. (5) Agent(s), if any. 2. The specific responsibilities of each person listed in any of the categories in Section a. 3. 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)
What Administrative information is required for amending the DMF?	For amending the original application following information shall be provided to FDA Name of DMF holder. DMF number. Name and address for correspondence. Affected section and/or page numbers of the DMF. The name and address of each person whose IND, NDA, ANDA, DMF, or Export Application relies on the subject of the amendment for support. The number of each IND, NDA, ANDA, DMF, and Export Application that relies on the subject of the amendment for support, if known. Particular items within the IND, NDA, ANDA, DMF, and Export Application that are affected, if known.
How DMF holder is communicated about his DMF Filing?	Once DMF is registered in Central Database, DMF Holder is send an email/letter which covers the following details: Number given to DMF in database and Type. Reminder to Submit all changes as amendments. Reminder to Notify FDA of change in holder name or address. Reminder to Notify FDA of change in agent/representative. Reminder to submit ANNUAL UPDATE (Annual Report). Submit Letter of Authorization (LOA) for each item referenced
When shall I submit annual report to my 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.

What will happen If annual update is not provided?	If annual update is not provided , it cause delays in FDA review of a pending IND, NDA, ANDA or any amendment or supplement to such application;
Does FDA send any reminders for annual update?	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
How DMF is registered at FDA	DMF is received by Central Document Room (CDR) staff. DMF entered into DMF Database, assigned a number, and a letter sent to the HOLDER.
What DMF holder shall do, if there is no response from FDA on submission of DMF?	If no response from FDA side, DMF HOLDER can put a query on the e-mail: dmfquestion@cder.fda.gov
What is the importance of Importance of LOA?	Sending LOA is the only mechanism which triggers the review procedure of DMF.
What I shall check before sending DMF?	Please check the following before sending DMF to FDA : 1.Check that address is correct: Central Document Room Center for Drug Evaluation and Research 5901-B Ammendale Road Beltsville, MD 20705-1266 2. Check that there is one original and one additional copy is in place. 3. Check that the Transmittal letters and Cover Letters are enclosed 4. Check that the submission is identified as Original sub mission or as supportive submission or as Amendment 5. Check that Type of DMF is clearly mentioned 6. Check the name and address of each sponsor, applicant, or holder, is clearly notified. 7. Check that Name, Title and signatures Signature of the holder or the authorized representative is in place. 8. Check that 2 Copies of LOA is enclosed with respect to specific applicant if known
When DMF is reviewed?	The DMF is reviewed only when requested by ANDA/NDA Reviewers at FDA office. When reviewer receives NDA/ANDA/IND application having a reference to DMF, he requests DMF from Central Documentation Room for review. It may take few days before he gets the copy of DMF
What is the action of Reviewer if he finds deficiencies in DMF?	When reviewer finds deficiencies in DMF, he communicates the deficiencies in detail to the DMF Holder. In addition he sends a formal letter to the applicant also.

Summary:

NDA and ANDA are basic regulatory submissions. They are reviewed in detail and manufacturing site is inspected by FDA before granting marketing authorization. DMF are just supporting submissions. The same are reviewed only in context with valid NDA/ANDA application.
The confidentiality of the information is strictly maintained by FDA for all types of submissions.
FDA is very transparent. It has dedicated facilities for communication with the applicant during the review procedure.

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