

Administrative Aspects of Managing a Drug Master File (DMF)

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DMF TYPES

- ❖ Type II is for Drug Substance, Drug Substance Intermediate, and Materials Used in Their Preparation, or Drug Product
- ❖ Type III is for Packaging Material
- ❖ Type IV is for Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
- ❖ Type V is for FDA-Accepted Reference Information. (Includes shared system REMS (Risk Evaluation and Mitigation Strategy))

Pre-Assigned DMF Number



- ❖ Obtain a Pre-Assigned DMF number before filing for a new DMF, except for Type V (see next slide for information)
- ❖ Request for a pre-assigned DMF number can be made through CDER NextGen Portal [NextGenPortal](#) or via email to cderappnumrequest@fda.hhs.gov. Do not send the same request to both. This will end up in receiving two different numbers for the same request. If this happens, send an email to dmfquestion@fda.hhs.gov requesting to cancel the duplicate number
- ❖ If you weren't notified with the pre-assigned number within 7 business days, send an email to dmfquestion@fda.hhs.gov asking for status

Clearance -Type V DMF



- ❖ The holder should get a clearance from the Agency prior to requesting a pre-assigned number for a Type V DMF. This includes Type V for REMS.
- ❖ Type V for sterile processing facility does not require clearance from the Agency
- ❖ Request for clearance should be emailed to dmfquestion@fda.hhs.gov with a letter of intent. It takes minimum of two weeks to get a response email from the Agency with a decision on the proposed submission
- ❖ The Letter of Intent should include the following:
 - Holder name and address
 - Proposed Subject (title) of the DMF
 - Specific information that will be in the DMF
 - Statement of why that information could not be submitted in an application
 - Clinical division(s) that should review the information, if applicable
 - If REMS, specify that in the letter of intent

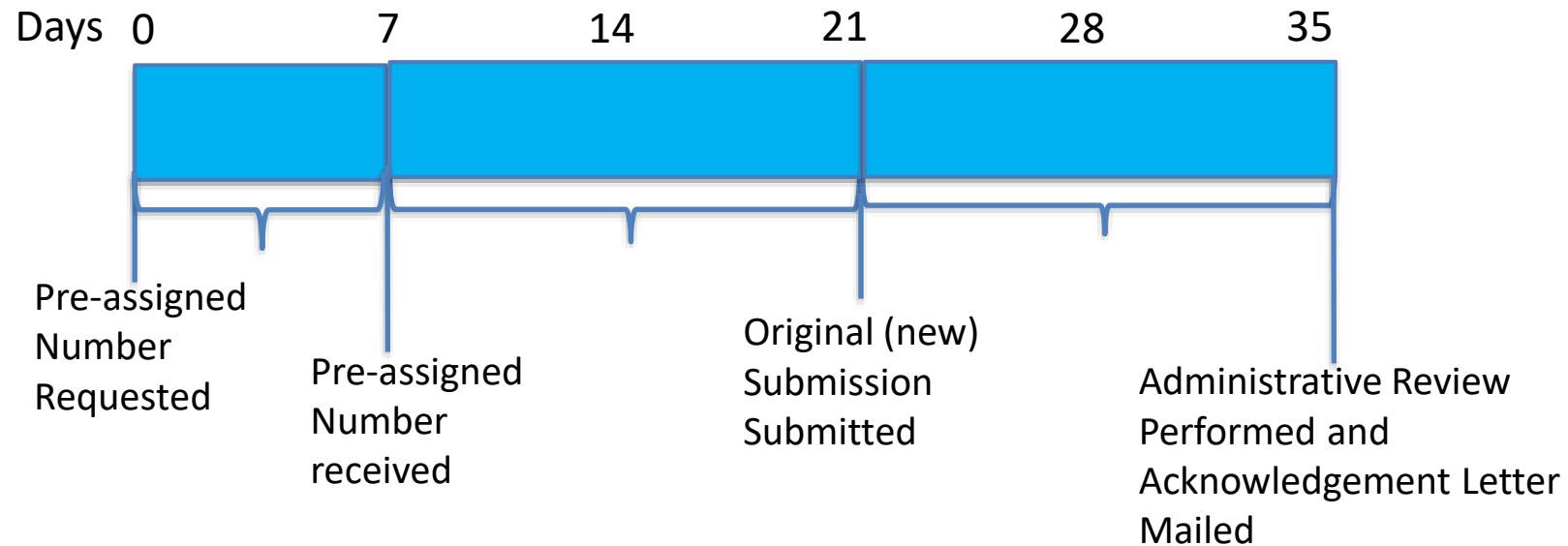
Submission Media



- ❖ Submission to Type II, IV or V DMF is expected to be submitted through the Electronic Submission Gateway (ESG) in electronic Common Technical Document (eCTD) format
- ❖ Type III DMF is exempt from the eCTD requirement. It can be submitted in paper (in two copies), in eCTD or non-eCTD format through the ESG. It can also be submitted in non-eCTD through the CDER NextGen Portal
- ❖ A 3rd Party Contractor can submit the submissions through the ESG on behalf of the holder but they cannot sign any submission documents such as the Cover Letter
- ❖ For more information, please see the separate presentation on electronic submissions

Original (new) Submission Timeline

- If an original submission is submitted within the two weeks of receiving the pre-assigned number, the DMF status can become active within the next two weeks, provided the original submission has no administrative filing issues



Original (new) Submission

- ❖ An Original (new) submission should include both Administrative and Quality (technical) information
- ❖ The Subject (title) of the DMF in the submission documents should be exactly what was in the request for the pre-assigned number (e.g., Cover Letter, Agent Appointment Letter, Letter of Authorization, DMF Statement of Commitment)
- ❖ An Administrative review is performed upon receiving the submission
- ❖ For the Type II DMF on a drug substance, a completeness assessment is done upon receiving the GDUFA fee payment and the DMF status is active
- ❖ A Quality (technical) review on a DMF is performed when an application (such as IND, NDA and ANDA) references a DMF
- ❖ See the separate presentation on Quality (technical) information

Administrative Documents to be included in the original submission

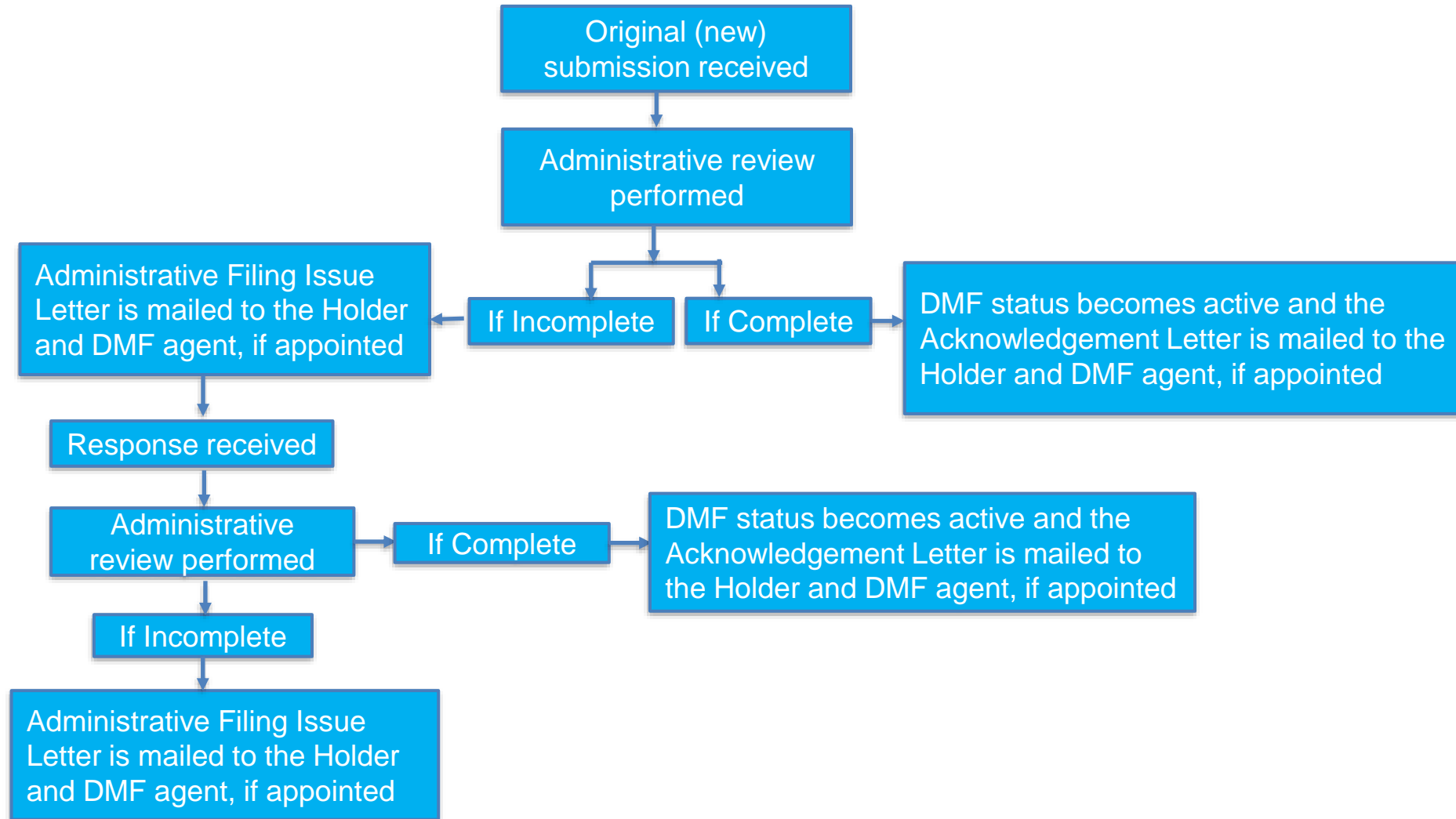
Cover Letter, DMF Statement of Commitment, Holder Responsibility Statement, Letter of Authorization, Agent Appointment Letter and Administrative Information Page

- ❖ **A Signed Cover Letter** – on a company letter head, with the DMF number, holder name and address, subject (title) of the DMF, DMF Type, submission information as ‘original’ and signed by the responsible official at the holder or agent company, whoever is submitting the submission
- ❖ **A Holder signed DMF Statement of Commitment** – on a company letterhead, stating that the DMF is current and the holder will comply with the statements made within it. DMF holder will notify FDA through an amendment to the DMF of any addition, change or deletion of information has been made to the DMF and will also notify the authorized party in writing that an addition, change, or deletion of information has been made to the DMF as required by 21CFR 314.420(c)
- ❖ **A Holder signed Agent Appointment Letter** – on a company letterhead (if appointed for a DMF)
- ❖ **A Holder signed Responsibility Statement** (if DMF holder is not the manufacturer) – on a company letterhead, stating that the DMF holder assumes full responsibility for the manufacturing of the material covered by the DMF
- ❖ **A Letter of Authorization** – on a company letterhead, if there is an authorized party who would incorporate information in the DMF by reference. For information, see the separate slide on Letter of Authorization
- ❖ **An Administrative Information Page** with the holder company name, address, contact person name, phone number, fax number, and email address; manufacturer name, site address(es), contact person name, phone number, fax number and email address; agent company name, address, contact person name, phone number, fax number and email address (if appointed)

DMF Acknowledgement

- ❖ If administrative review of the original (new) submission found to be complete, an Acknowledgement Letter is sent (via postal mail) to the holder and agent (if appointed) and the DMF status becomes 'active'
- ❖ If administrative review of the original (new) submission found to be incomplete, an Administrative Filing Issue Letter requesting the required information is sent (via postal mail) to the holder and agent (if appointed)
- ❖ Once the response to administrative filing issue is received with the requested information and if complete, an Acknowledgement Letter is sent (via postal mail) to the holder and agent (if appointed) and the DMF status becomes 'active'
- ❖ DMF Acknowledgement Letter is mailed to the holder and agent only for the original submission when the DMF status becomes active, not for any subsequent submissions such as an amendment, Letter of Authorization, and Annual Report

Original (new) Submission Process Flow



Subsequent Submissions

- ❖ A subsequent submission is any submission submitted after the original submission, such as an Amendment (administrative & Quality (technical)), Letter of Authorization and Annual Report
- ❖ An administrative Amendment is reporting any new changes made to the administrative content of the DMF (such as holder, manufacturer & agent information, DMF Type, Subject (title) and authorized party)
- ❖ A quality amendment is reporting any new changes made to the technical content of the DMF
- ❖ A signed Cover Letter need be submitted with every submission
- ❖ An Administrative Information Page
- ❖ If any submission to a DMF is administratively incomplete, an administrative filing issue letter requesting the required information will be sent (via postal mail) to the holder and agent (if appointed).
- ❖ An Administrative Review is performed through out the life cycle of a DMF

Letter of Authorization (LoA)

- ❖ A Letter of Authorization is a letter from a DMF holder authorizing an applicant (such as IND, NDA and NDA) or another DMF holder to incorporate information in the DMF by reference, and also authorizes the FDA to review the DMF
- ❖ A Letter of Authorization should be submitted to the DMF and a copy of the letter should be sent to the authorized party
- ❖ A LoA should be on a company's letterhead. For Information need in a LoA, please refer to the template that is in the DMF website (link is provided in the last slide)
- ❖ A LoA should be submitted even if the DMF holder is the authorized party
- ❖ A LoA does not give an authorized party the permission to view or access a DMF

Letter of Authorization (LoA) (cont'd)

- ❖ A LoA with multiple authorized parties is not accepted. If there is more than one authorized party, submit a separate LoA for each party
- ❖ If any information in the LoA has changed (such as holder name or authorized party name), a new LoA should be submitted to the DMF and a copy of the letter should be sent to the authorized party
- ❖ When a holder name changes, a new Letter of Authorization with the new holder name should be submitted to the DMF for each current authorized party
- ❖ If the holder has more than one DMF and has a current authorized party in each DMF, they need to submit a new LoA with the new holder to each DMF separately

Annual Report

- ❖ An Annual report should be submitted to the DMF every 12 months even if no amendment was submitted
- ❖ The Annual report should not notify any new changes made to the DMF; new changes (either administrative or quality) should always be reported to the DMF only by an amendment
- ❖ If an annual report was not submitted for three consecutive years, the Agency will send an overdue notice letter (via postal mail) to the holder and agent (if appointed) reminding them to submit an annual report within 90 days

Annual Report (cont'd)

The Annual Report should contain

- ❖ A list of amendments (with date) submitted since the last Annual Report or the original submission date, whichever is most recent OR a statement that no amendment was submitted (no need to resubmit the amendment)
- ❖ A complete list of current authorized party names OR a statement that there is no authorized party
- ❖ A List of parties' whose authorization has been withdrawn, if applicable
- ❖ A Holder signed DMF Statement of Commitment
- ❖ An Administrative Information Page with the current contact information of DMF holder, manufacturer and Agent (if appointed)

DMF Holder



- ❖ Only one person/entity can be the holder of a DMF
- ❖ DMF Holder contact person should be an employee of that company not from one of their subsidiary companies
- ❖ DMF holder and the DMF agent should retain a complete reference copy that is identical to their submissions to FDA
- ❖ DMF holder is responsible for the content of the DMF

DMF Holder (cont'd)

- ❖ When it is a holder name change, submit a holder signed letter notifying that it is an internal holder name change from x to y (for e.g. from ABC Pharmaceutical Company to XYZ Pharma Company)
- ❖ When it is a transfer of DMF from one holder to another, submit a holder transfer letter from the previous holder and a holder acceptance letter from the new holder
- ❖ When a DMF is transferred from one DMF holder to another, all documents associated with the DMF should be transferred to the new DMF holder
- ❖ Whether it is an internal name change or a change of holder, the following documents should be submitted along with the amendment: a signed DMF statement of commitment with the new holder name, agent appointment letter with the new holder name (if appointed), letter of authorization with the new holder name (if there is a current authorized party) and an administrative information page with the current contact information
- ❖ If the holder has more than one DMF, they need to be submitted to each of DMF separately

DMF Agent

- ❖ Although there is no regulatory requirement to appoint an agent for a DMF, the Agency strongly suggests that non-US holders appoint an agent
- ❖ An agent for DMF purposes is not the same as an agent for the purposes of the Drug Listing and Registration System (DRLS), but the holder can appoint the same agent for both. A separate Agent Appointment Letter should be submitted to the DMF
- ❖ An Agent Appointment Letter should be on a holder company's letterhead and signed by the responsible official at the holder company
- ❖ A Holder signed Agent Appointment Letter should include holder name, address, contact information, DMF number (if pre-assigned), Subject (title) of the DMF, agent company name, address, contact person name, phone number, fax number (if available), email address and agent's role specific to the DMF
- ❖ When an information in the Agent Appointment letter has changed (such as agent company name, address, contact person information or holder name), a new Agent Appointment Letter should be submitted to the DMF

Reactivation

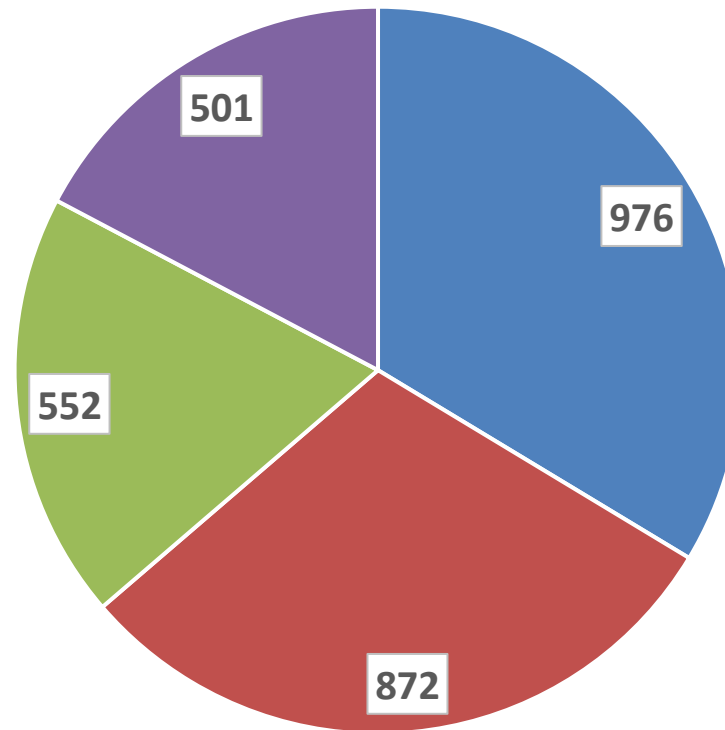
- ❖ To reactivate the closed DMF, submit the following:
 - A Holder signed Letter requesting to reactivate the DMF
 - A Holder signed DMF Statement of Commitment
 - An Agent Appointment Letter, if appointed
 - A Letter of Authorization (if there is a current authorized party)
 - A Holder Responsibility Statement if the holder is not the manufacturer of the material covered by the DMF
 - If it has been a while since the DMF was closed, the Agency recommends the holder submit a complete update of the quality information
- ❖ For the detail on administrative documents, check the slide titled, 'Administrative documents to be included in the original submission'

Reactivation (cont'd)

- ❖ The FDA does not close a Type II DMF if the GDUFA fee has been paid
- ❖ Currently, you can reactivate the closed DMF. Once the draft DMF Guidance becomes final, you cannot reactivate the closed DMF, you may need to file a new one
- ❖ Currently, reactivating the closed Type II DMF will not incur a new GDUFA fee if a fee has already been paid. This will change when the draft DMF Guidance becomes final. In that case, if the holder closes their Type II DMF for which a fee has been paid, they cannot reactivate the closed DMF, they need to file a new DMF and pay the fee again

DMF Administrative Review Statistics

2019



■ DMF Acknowledged

■ Administrative Filing Issue Letter Sent

■ Response Rec'd

■ Annual Report Overdue Notice Sent

Common Administrative Issues found in the submissions

- ❖ Discrepancy in the DMF number, holder, manufacturer or agent information, Subject (title) of the DMF, DMF Type or authorized party
- ❖ DMF Statement of Commitment was not signed by the Holder
- ❖ Annual Report is not submitted every 12 months
- ❖ If responding to a filing issue, the Cover Letter does not specify that it is a response to administrative filing issue

Common Administrative Issues found in the submissions (cont'd)



- ❖ Letter of Authorization was not submitted to the DMF when there is a current authorized party
- ❖ Authorized party name in the annual report does not match to what is in the Letter of Authorization
- ❖ When a holder name or authorized party name changes, a new Letter of Authorization was not submitted to the DMF
- ❖ When a holder name or the agent information changes, a new Agent Appointment Letter (if appointed) was not submitted to the DMF
- ❖ When a holder name, address or contact information changes, an amendment notifying the change was not submitted to the DMF

Resources



DMF Website (draft Guidance document):

<https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs>

Pre-assigned DMF Number Request:

<https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number>

ESG Website: <https://www.fda.gov/industry/electronic-submissions-gateway>

eCTD Website:

<https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd>

DMF Submission Inquiry: dmfquestion@fda.hhs.gov

Secure Email: <http://inside.fda.gov:9003/it/ITServices/FDAEmail/ucm647658.htm>

Acknowledgement



CDR David Skanchy, Division Director, DLAPI

Thank You

- For questions regarding the content of this presentation, please type them into the 'Q&A Box' in the bottom right hand corner of your screen so that we can address them during the scheduled Q&A panel after this session.
- If you have any questions on this presentation after the workshop is over, please send them to the email DMFWorkshop2021@fda.hhs.gov by March 19, 2021 for inclusion in the follow-on webinar on April 9, 2021.

