SBIA-DMF Drug Substance Workshop

March 3 & 4, 2021 (Virtual)

Communications to DMF Holders and Applicants throughout the DMF Lifecycle

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PURPOSE

An overview of the types of communication that may be sent by DLAPI to holders or applicants during the DMF lifecycle.

OBJECTIVES

Understand the types of communication and actions required by the DMF holder or applicant for each letter during the DMF life cycle per GDUFA II.

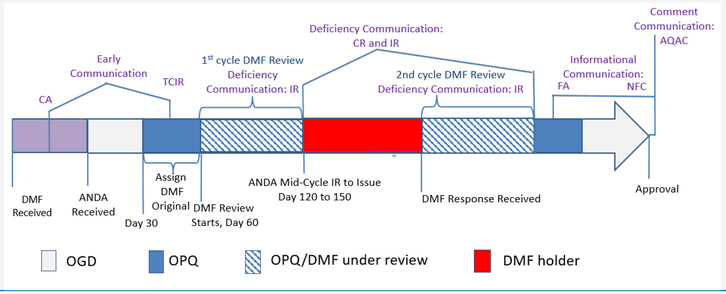
- **Early communications (CA, TCIR),**
- **Deficiency and comments communications (CR, IR, AC), and**
- **Informational communications (FA, NFC).**

Discuss the kind of issues that may delay DMF adequacy and therefore an approval of ANDA.

Highlight the importance of communication with both the Agency, the referencing ANDAs, and any secondary DMF holders.

METHOD

At what stage does each type of letter apply?



RESULTS

Type of Letters	Suggested DMF Holder Response Time	Review Times	Purpose of the Letter
Completeness assessment (CA)	30 days	1st Cycle: 60 days (from the latter of the date of DMF submission or DMF fee payment); 15 days for subsequent cycles	To inform the holder that there not sufficient information for a scientific review
GDUFA Complete Response (CR) •Major •Minor	30 days*	Minor: 30 to 60 days Major: 60 to 90 days**	To inform the holder of deficiencies in the submission
Deficiency •Secondary DMFs	30 days	30-90 days**	Same as a CR letter Secondary must be adequate for the Primary DMF to be adequate
Additional comment (AC)	30 - 60 days***	30 days	Prevents minor comments to the holder without delaying ANDA approval
Information request (IR)	Usually one to two weeks	During DMF review period	To resolve deficiencies without going through a CR letter
First Adequate letter (FA)	No response required	N/A	To communicate to the holder that the DMF is adequate for the first time To prevent late-cycle unsolicited amendments to the DMF that are disruptive to the ANDA approval process.
No Further Comments Letter (NFC)	No response required	N/A	To signal that both the DMF is adequate and that the ANDA is approved or tentatively approved
Type of Letter	**Response Timeline for ANDA Applicant**	**Review Times**	**Purpose of the Letter**
Timely Consults and Information Request (TC-IR)	30 days	N/A	To prevent the delay of ANDA due to a hidden DMF facility To internally identify issues that take longer time to resolve
***Considered late if received with less than 90 days before GD (minor) or 120 days before the GD (major); **longer if P/T consult involved; **contact DMFOGD if longer than 60 days**			

CONCLUSIONS

DMF review is part of the overall ANDA review process. Understanding DLAPI's letter communication strategies will help you make well informed decisions for your DMF and understanding the effect of the referencing ANDA applications. Please respond to all letters in a timely manner and provide a complete response to any deficiencies or comments.

BE PROACTIVE! Remember that if you have any questions or concerns with meeting due dates please reach out to DMFOGD@FDA.HHS.Gov.

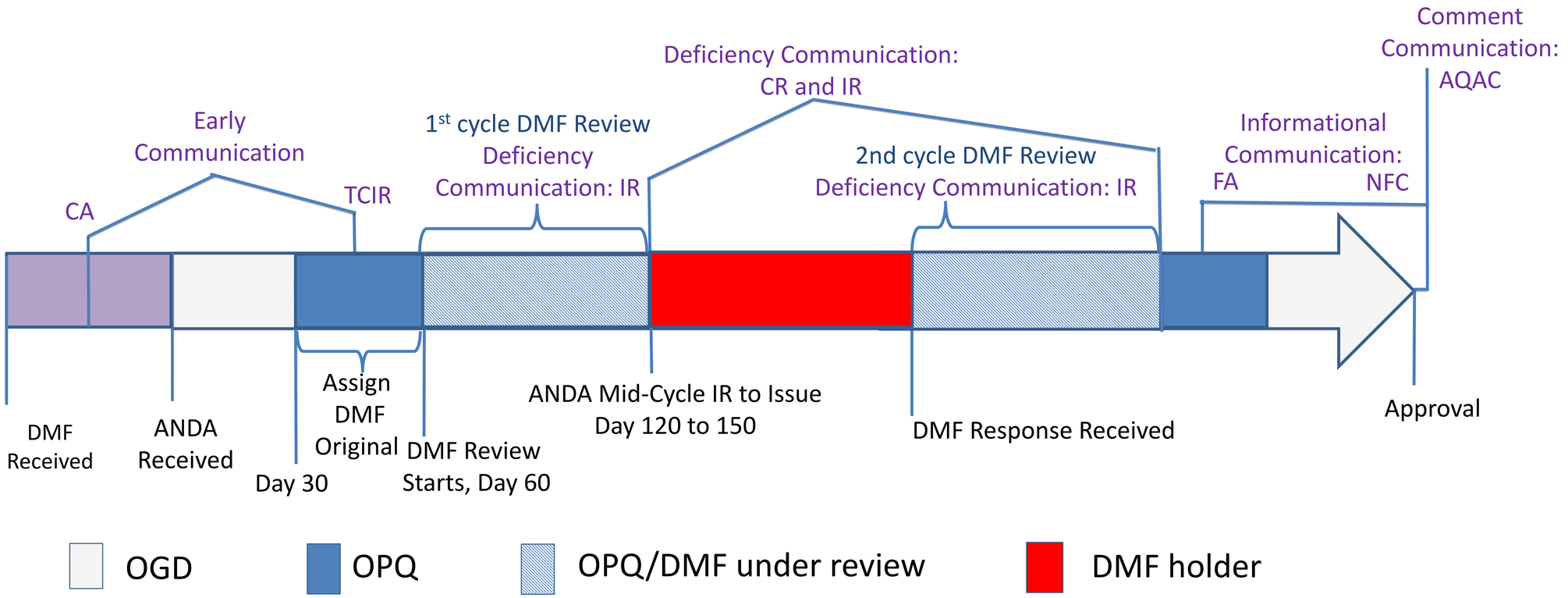
Special Acknowledgment to Jayani Perera and Wei Song

Communications with Holders and Applicants throughout the DMF Life-cycle (summary)

Fatima C. Sequeira - Chemist
Division of Lifecycle API
Office of New Drug Products
Office of Pharmaceutical Quality, FDA/CDER

Vathsala Selvam – Technical Information Specialist
Claude Theophin – Technical Information Specialist
Terrence Nichols – Management Support Specialist
CDR Ben Danso – Program Manager, Office of Program & Regulatory Operations
CDR David Skanchy – Director of DLAPI

Importance of Comprehending Timelines



The DMF review timeline is nested into the ANDA applicant's timeline.

Responding to letters appropriately will increase the likelihood of first-cycle ANDA approval.

Early Communication: Protecting the Timeline

Completeness Assessment

Letter Sent to DMF Holder

- To inform the holder there is not sufficient information for the DMF to undergo scientific review.
- FDA strongly encourages the DMF holder to submit a complete DMF and pay the DMF fee at least 6 months prior to the submission of an ANDA or PAS that will rely on the DMF.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/completeness-assessments-type-ii-api-dmfs-under-gdufa-guidance-industry

From 1/1/20 to 10/27/20
1st cycle CAs sent: 254
2nd cycle CAs sent: 99
3rd cycle CAs sent: 12

Timely Consults and Early IR (TC-IR):

Letter Sent to Applicant

- Identify hidden facility early in the ANDA review process, that there is sufficient time for facility evaluation and inspection.
- ANDAs 356H should have the following DMF facilities listed:
  - Conduct any part of the DMF process.
    Examples of manufacturing sites include:
    - Non-Sterile API by Chemical Synthesis
    - Sterile API by Chemical Synthesis
    - Chemical Sterilization
    - Plant/Animal Extraction Purified API
    - Non–Sterile API by Fermentation
    - Sterile API by Fermentation
    - Micronization
  - Conduct any drug substance specification testing
  - Manufacture a critical fragment through a secondary DMF, or intermediate vendor
- Identify issues that take longer to resolve (Impurity qualification, duration of use, MDD).

	FY18	FY19	FY20	FY21 (to 11/2020)
Total TCIR completed	1255	1065	1036	826
# of IR letters issued	193	128	96	78

Deficiency Communications

First cycle ANDA approval will most often be achieved when the holders timely respond to CR letters, communicate with the applicant, and communicate with any secondary DMF holders or intermediate vendors.

98% of DMFs being reviewed for the first time are found to be inadequate and are issued a CR letter.

Fiscal year	FY15	FY16	FY17	FY18	FY19	Total
# of DMF first cycle deficiency letters	262	247	356	360	247	1492
Median days to receive response to Deficiency Letter	137	121	123	82	101	110
Median # of Deficiencies issued per letter	12	11	11	11	12	11

Recommendations:

- Respond to your CR/IR letters within the timeframe indicated in the letter
- Answer deficiencies and comments in the CR/IR letter.
- Request an email exchange if you have questions about deficiencies or comments (within 20 business days from the letter date), send request to DMFOGD@fda.hhs.gov
- Confirm secondary DMFs (non-API type II) status. Remember that secondary DMFs have to be adequate before the primary DMF can be deemed adequate
- Avoid unsolicited amendments in the last third of an ANDA review cycle as it could interfere with the ANDA timeline.

Comment Communication

Every six months since October 2018, 175 Adequate with Additional Comment (AQAC) letters have been sent by DLAPI	
Types of Request	Minor comments that will not impact the drug substance specification, impurity profile, or relate to PGIs
Benefit to the Stakeholders	AQAC letters are issued after ANDA action is taken. This prevents low risk comments from delaying an applications approval. If there are multiple referencing ANDAs, DLAPI will track all applicants and find a suitable time to issue a AQAC letter to avoid interference with action taken on a refencing ANDA
Actions DMF holders should take	Respond to these letters timely (30-days) DMF holders should coordinate with the ANDA applicant(s) before responding to an AC letter. If the response will take longer than 60-days contact DMFOGD@FDA.HHS.Gov to determine if the response might interfere with an action timeline for a referencing application. After 6-months, these comments can be converted to deficiencies and a CR letter may be issued.

Top 10 comments in AQAC letters 41 AQAC letters, with 69 comments (October 2020)	
10	Failure to provide updated long-term stability data or revised stability specifications after an amendment (12)
9	Q3D inquires (9)
8	Failure to provide COAs for intermediates or reagents after an amendment (8)
7	Failure to update the submission after an amendment, specifically in S2.2, MBR/EBR, or impurity tables (8)
6	Minor typographical errors: mismatch information, illegible, chemical names, calculations, and batch numbers (8)
5	Missing facility information: FEI; cGMP statements, and clarification of facilities function (7)
4	Failure to update reference standard COAs after an amendment (5)
3	Use/Clarification of recovered solvent or reprocessing step (4)
2	Missing supportive analytical method information: RRT, LOD/LOQ, system suitability (4)
1	Other (4)

Informational communications

First Adequate Letter (FA):

- An FA letter is sent to the DMF holder the first time the DMF becomes adequate.
- It serves as a signal to the DMF holder not to send late-cycle, unsolicited amendments, which may disrupt the ANDA approval process.
- AQAC letters can be received before or after FA letter is issued.
- Issued 30 days after the DMF review is deem adequate.
- About 201 FA letters have been sent (1/2020 -11/2020)

No Further Comment Letter (NFC):

- An NFC letter is sent to the DMF holder when both the DMF and referencing applicant is approved or tentatively approved.
- AQAC letters can be received before or after an NFC letter is issued.
- Issued 30 days after the ANDA is approved.
- 970 NFC letters have been sent (DMFs can support multiple ANDAs)

Any questions about the status of your DMF, please reach out to DMFOGD@fda.hhs.gov

DLAPI Letter Approach

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General Reminders

- Provide responses to all deficiencies or comments in your letters.
- Clearly state when data is provided in an appendix and make sure the location is provided.
- Confirm that all critical facilities listed in S.2.1 Manufacturers are listed in the 356H of the referencing ANDA.
- Keep the naming of your DMF subject and DMF title the same.
- If you have issues with your eCTD, please contact Electronic Submissions Team at esub@fda.hhs.gov
- Provide a copy of the LOA for each DMF and each referenced party
- Remember that if you have any questions or concerns related to due dates, please reach out to DMFOGD@fda.hhs.gov, preferably through a secured email address.

Be Proactive

Thank You!

- Send questions regarding this poster to: DMFWorkshop2021@fda.hhs.gov by February 15th for inclusion in the poster Q&A session on March 4th
- Follow-on webinar for both posters/presentations on April 9th. Questions can be sent to the above email by March 19th for the webinar.
- Please refer to the following posters for cross-referenced materials: Administrative Process (V. Selvam)
- Please refer to the following presentations on March 3rd for additional information: Effective communication strategies (D. Skanchy)