

Effective Communication Strategies For Drug Master Files (DMF)

CDR David Skanchy – Director

Division of Lifecycle API

Office of New Drug Products

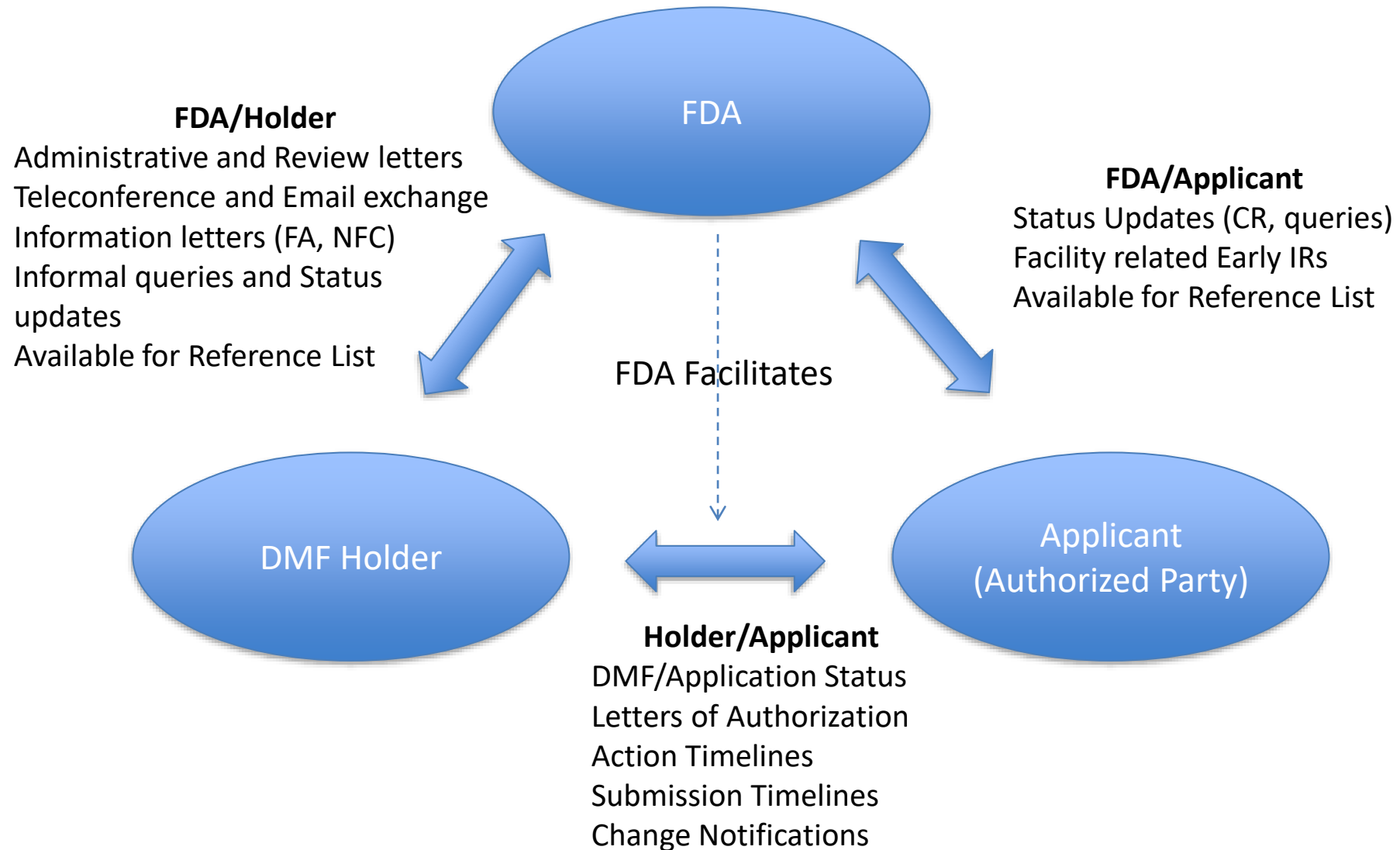
Office of Pharmaceutical Quality, FDA/CDER

CDR Ben Danso – Lead DMF Project Manager

Office of Program and Regulatory Operations

Office of Pharmaceutical Quality, FDA/CDER

Communication Pathways



What information can FDA share?

- DMF Holder
 - Public Information (e.g. Available for Reference list, Quarterly DMF Inventory list)
 - Status Information
 - Confidential Administrative Information, fee, or Completeness Assessment
 - Confidential Review Information or technical DMF information
 - *Cannot share confidential application status information (e.g. Goal Dates)*
- Applicant
 - Public Information (e.g. Available for Reference list, Quarterly Inventory DMF list)
 - Status Information
 - *Cannot share confidential administrative or review information*

Formal and Informal Communication

- Formal Communication
 - Review letters (e.g. CR, IR, AC, DMF Incomplete)
 - Informational letters (e.g. FA, NFC, General Advice)
 - Formally granted teleconferences
 - Formally granted email exchanges
 - Controlled Correspondence
- Informal Communication
 - Communication outside of formal communication channels
 - Responses to email queries
 - Responses to voice queries

DMF Complete Response (CR) Letter

- GDUFA DMF Complete Response Letter:
 - Issued for **TYPE II** API DMF for ANDAs (only).
 - Includes deficiencies from all review disciplines, including consults.
 - Includes DMF facility status information.
 - Includes deficiencies in **Section A**, and comments in **Section B**.
- CR Letter issuance timelines:
 - Issued one to three weeks before the mid-cycle due date (QDD1) or one week before the end-of-cycle due date (QDD2)
- Regulatory status of a DMF after CR Letter issued:
 - DMF is inadequate and cannot support an approval action.
- Review status of DMF after CR Letter issued:
 - DMF review cycle closes when the letter issues (i.e. can support a CR action on a referencing ANDA).

DMF Complete Response (CR) Letter

- Response timeline:
 - Is indicated in the letter. Missed timeline is considered a **late** response.
 - Timeline is impacted by MAJOR/MINOR deficiencies (120 days or 90 days before a Goal Date).
 - DLAPI does not guarantee an additional review cycle for late responses.
- Notification of CR should be provided as instructed (DMF-OGD mailbox).
- Both Teleconference (**1st Cycle ONLY**) and Email Exchange options are available
 - follow instructions in the letter.
- Extension Requests:
 - Indication that you cannot respond by the requested date.
 - Request may be qualified as “Deny” or “Grant”.

DMF Deficiency Letter

- DMF Deficiency Letter:
 - For DMFs referenced by other DMFs (i.e. Secondary DMF) or INDs/NDAs
 - Includes Chemistry deficiencies, and at times other disciplines.
 - ***No facility status information***
 - Notification of Response should be provided as instructed (DMF-OGD).
- Letter Timelines:
 - Issued one to three weeks before the mid-cycle due date (QDD1) or one week before the end-of-cycle due date (QDD2)
- Review and Regulatory status of the DMF:
 - Review cycle is closed. The DMF is inadequate and cannot support an approval action, but can support a CR action on a referencing ANDA.
- Response timeline is indicated in the cover sheet of the letter. Missed timeline is considered a ***late*** response. **No** Teleconference for Secondary DMF. Email Exchange option is available.

DMF Information Request Letter

- Issued to communicate deficiencies in cases where the holder should be able to respond quickly and get the DMF to an adequate status.
- Usually issued relatively late in an ANDA review cycle (30 days before a QDD) when ANDA approval is a likely outcome.
- Regulatory and review status of the DMF:
 - DMF is pending and cannot support an approval action until issues are resolved.
 - DMF review cycle remains open (i.e. review is not finalized) and response is reviewed upon receipt.
- We err on the side of giving the DMF holder an opportunity to respond. Do your best to respond in the allotted time (usually 10 to 30 days) and let the RBPM know if you cannot!

DMF Additional Comment (AC) Letter

- Issued to communicate very minor comments that **do not** make the DMF inadequate and can support an approval action.
- Review status:
 - DMF review cycle closes with an adequate recommendation. Can trigger an FA letter if appropriate.
- We now issue these after the ANDA action so that a response does not open another review.
- Please respond to these within 60-days if possible. If a response will take longer than 60-days please email DMFOGD to ensure a response will not interfere with an action timeline.

DMF Incomplete Letter

- Issued to communicate information needed to pass a Completeness Assessment.
- Regulatory status of the DMF:
 - Incomplete and not eligible for the **“Available for Reference List”** which precludes the filing of a reference application.
- Review status:
 - DMF CA review cycle closes with an incomplete status.
- There is no set timeline for a response but we recommend responding as quickly as possible.
- **Please always notify the DMFOGD mailbox as instructed in the letter when you submit your response**

Informational Letters

- **DMF First Adequate Letter**
 - New under GDUFA II.
 - Issued when a DMF reviewed under GDUFA is found adequate for the first time.
 - Target to issue within 30-days of the finalization of the review finding the DMF adequate for the first time.
 - Issue over 300 annually.
- **DMF No Further Comment Letter**
 - Issued to the DMF holder when the referencing application is approved.
 - Target to issue within 30-days of approval action on the referencing ANDA.
 - Issue about 1000 letters annually.
 - When there is a letter backlog, the FA letters have the higher priority.

Tip – If you think you are owed an FA or NFC letter contact DMFOGD mailbox

Teleconferences

- FDA will grant teleconferences when requested to clarify **1st Cycle** DMF deficiency letters **only**.
- DMF holders must request such teleconferences in writing within **20 business days of CR letter receipt**, for specific issues to be addressed.
- For detailed information on the T-con process please see the poster “Teleconference Process Outline” by Benjamin Danso and Jayani Perera.

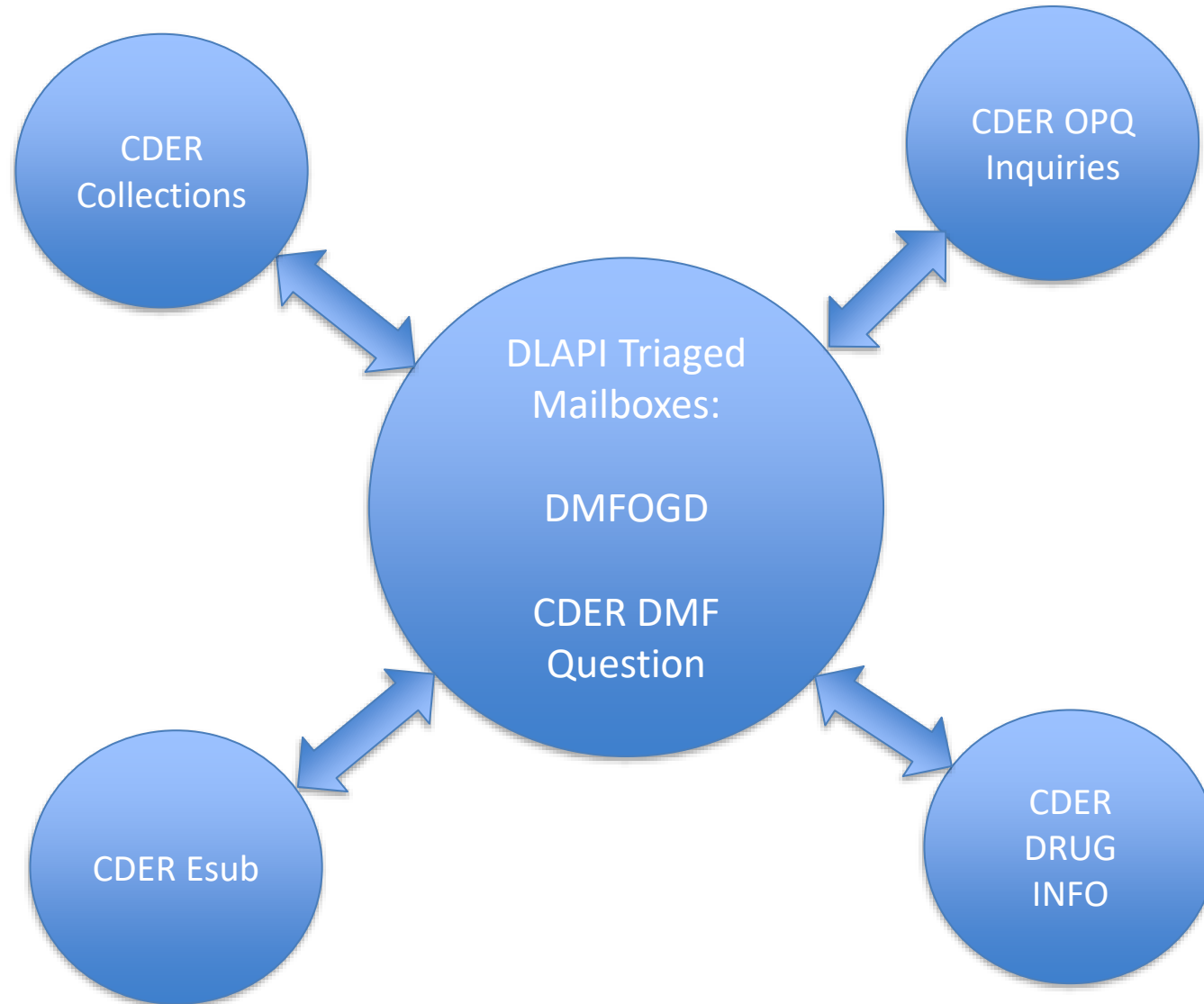
Email Exchange

- Introduced in GDUFA II and is the preferred communication pathway by industry regarding deficiencies (10:1 ratio).
- Issue the response within **30-days** of receiving the Initial Email Exchange request (typically we are faster).
- We will respond to Email Exchange requests generated from any cycle (i.e. not limited to first cycle) or type of letter issued (e.g. DMF Deficiency letter for a secondary DMF).
- We prefer to receive these requests within 20-business days but we will not deny the request if later.
- Eligible for one follow up exchange after receiving the initial response.

Informal Communication Benefits

- Receive quick answers
 - Responses typically provided in one to three days
- Appropriate for a wide variety of queries
 - Great for status updates
 - Great for answers to non-review related technical questions
 - DLAPI responds to about 3000 informal queries via email annually
 - 90% of the informal queries we receive are appropriate
- Informal Communication is a good place to start
 - All queries are triaged so they get sent to the appropriate SME
 - We respond with appropriate mailbox information if a request is outside our areas of expertise
 - We will route you to an appropriate communication mechanism if an informal response is not appropriate (e.g. referred to a Controlled Correspondence)

Email Query Processing in DLAPI



Tips for Sending Effective Emails

- Send your query to a single FDA email inbox
- Clearly identify yourself and your role (i.e holder, agent, authorized party)
- Use your company email account
- Provide as much detail as possible
 - Include appropriate attachments
 - Use/check correct references to specific DMF and application numbers
- Avoid framing queries as hypotheticals when possible

Use DMFOGD@FDA.HHS.GOV for the following types of queries:

- DMF review status updates
- Response notifications as instructed in our letter templates
- Technical or policy questions related to API review
- GDUFA questions related to DMFs (some fee related questions will require OM input)
- Facility related questions (we will have to reach out to OPMA or OC for some issues)
- Questions about NFC and FA letters
- Email Exchange Requests and Teleconference Requests
- Queries about Completeness Assessments the “Available for Reference” list
- Any time you just can’t figure out where to send the query and its somehow related to a DMF or API

Use dmfquestion@fda.hhs.gov for the following types of queries:

- General queries about DMFs
- Administrative queries about DMFs
- Questions about FDA forms and letter templates for DMFs
- General questions based on information on the FDA DMF webpage
- Questions about submitting Type V DMFs
- Questions about Type III and IV DMFs

Controlled Correspondence

- When an informal response is not appropriate we may refer you to submit a Controlled Correspondence
- Typically occurs when an issue involves new policy, precedent, or pending guidance
- Have response timelines and metrics set by GDUFA
- Controlled Correspondence are submitted to OGD with quality issues referred to the Office of Policy for Pharmaceutical Quality (OPPQ) within OPQ
- DLAPI subject matter experts work with OPPQ to draft answers to Controlled Correspondence

Controlled Correspondence

- During FY 2020, OPQ responded to ~ 815 Controlled Correspondences (CC's)
- Approximately 50 of those CC's asked drug substance questions
- The most frequently asked questions were in the following categories:
 - Impurity limits
 - Acceptability of starting material
 - Sameness (polymorphism, salt forms, solvates, etc.)
 - Alternate drug substance manufacturing site
 - Alternate drug substance supplier

Effective Communication Between Applicants and DMF holders

- Critical for a smooth and efficient review process
- Helps avoid unnecessary delays to approvals (i.e. goal date extensions)
- FDA role is to facilitate Applicant/DMF Holder communication by providing relevant information to both parties
- Actual communication is up to YOU!
- From the FDA perspective poor communication is often a barrier for first cycle approvals

Communication Between Applicants and DMF holders – Unsolicited Amendment Issues

- Poorly timed unsolicited amendments continue to adversely impact application timelines
- Can result in goal date extensions or unnecessary CR letters (to DMF and applicant)
- Most unsolicited amendments do not need to be submitted at the particular time they are received
- Communication between the applicant and DMF holder regarding the DMF submission and application timelines is the solution

Communication Between Applicants and DMF holders – Facilities

- Accurate facility information is critical for a timely application review
 - Facility evaluations and inspections require planning
 - DMF related facilities discovered late in a review process adversely impact approval actions
- FDA uses the TCIR process to help avoid adverse consequences of hidden facilities but this is an industry responsibility
- Applicants need to have visibility on all facilities that impact their application
 - Manufacturing and routine release and stability sites
 - Clarity provided in LoAs when there are facilities in the DMF not being used for a particular application
 - Manufacturing sites include critical intermediates (late stage intermediates)
 - FDA cannot share DMF related facility information with an applicant if the facility is not included in their application

Helpful Links

- Email Addresses
 - DMFOGD@fda.hhs.gov
 - dmfquestion@fda.hhs.gov
 - CDER-OPQ-Inquiries@fda.hhs.gov
 - CDERCollections@fda.hhs.gov
 - esub@fda.hhs.gov
 - SecureEmail@fda.hhs.gov
- FDA Guidance
 - DMF Guidance (draft): <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-master-files-guidance-industry>
 - ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA : <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/anda-submissions-amendments-abbreviated-new-drug-applications-under-gdufa>
- Controlled Correspondence Related to Generic Drug Development (NextGen portal):
 - https://edm.fda.gov/EDMIDPLogin/welcome?response_type=code&client_id=0oa1as7rb2poiYTch297&scope=openid%20profile&state=20637600_1611231479919&redirect_uri=https%3A%2F%2Fedm.fda.gov%2Foidcclient%2Fedmrp

Thank You!

- Please type your questions into the chat box provided for inclusion in the Q and A panel at the conclusion of this session.
- For questions after the session, please send to: DMFWorkshop2021@fda.hhs.gov by 3/19/2021 for inclusion in the follow-on webinar on April 9, 2021.
- Please refer to the following posters for related content:
 - “Teleconference Process Outline” by Ben Danso and Jayani Perera.
 - “Communications to holders and applicants throughout the DMF life-cycle” by Fatima Sequeira, et al.
- Please refer to the following presentations on March 3rd and 4th for related content:
 - “Timely Consults and Early IR (TCIR)” by Jayani Perera
 - “Drug Substance Facilities – Hidden and Critical Intermediate” by Wei Liu
 - “Major and Common Deficiencies in DMFs” by Wei Liu