

# GDUFA II UPDATE AND DMF STRATEGIES TO SUPPORT FIRST-CYCLE APPROVALS

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*Generic and Biosimilar Medicines Conference  
4 November 2019, North Bethesda, Maryland*

**A quality product of any kind consistently meets the expectations of the user.**



**A quality product of any kind consistently meets the expectations of the user.**



**Drugs are no different.**

A close-up photograph showing a hand holding an orange pill bottle, pouring three white, oval-shaped pills into the palm of another hand. The background is softly blurred, focusing attention on the action of dispensing medication.

**Patients expect safe and effective  
medicine with every dose they take.**

A close-up photograph of a person's hands. The left hand is holding an orange plastic pill container, tilted to pour three white, oval-shaped pills into the palm of the right hand. The background is softly blurred, showing a person's arm in a light blue sleeve.

**Pharmaceutical quality is**  
assuring *every* dose is safe and  
effective, free of contamination  
and defects.



**It is what gives patients confidence  
in their *next* dose of medicine.**

# GDUFA II: DMF Program Enhancement

- Communication of DMF Review Comments
- Teleconferences to Clarify DMF First Cycle Review Deficiencies
- DMF First Adequate Letters
- DMF No Further Comment Letters
- Guidance on [Post-Approval Changes to Type II API DMFs](#) (Sept 2018)

# DMF Quality Assessment Process

Introduction

DMF Timeline

Communication

Improvement

- **DMF Quality Assessment Timeline**
  - Timeline with respect to the ANDA process
  - DMF Communication timepoints
- **Communication**
  - Communication types
  - Anticipated response timeframe
- **Improvement Areas**
  - Types of significant deficiencies
  - Mitigation steps

# DMF Timeline – Original/New DMF Example

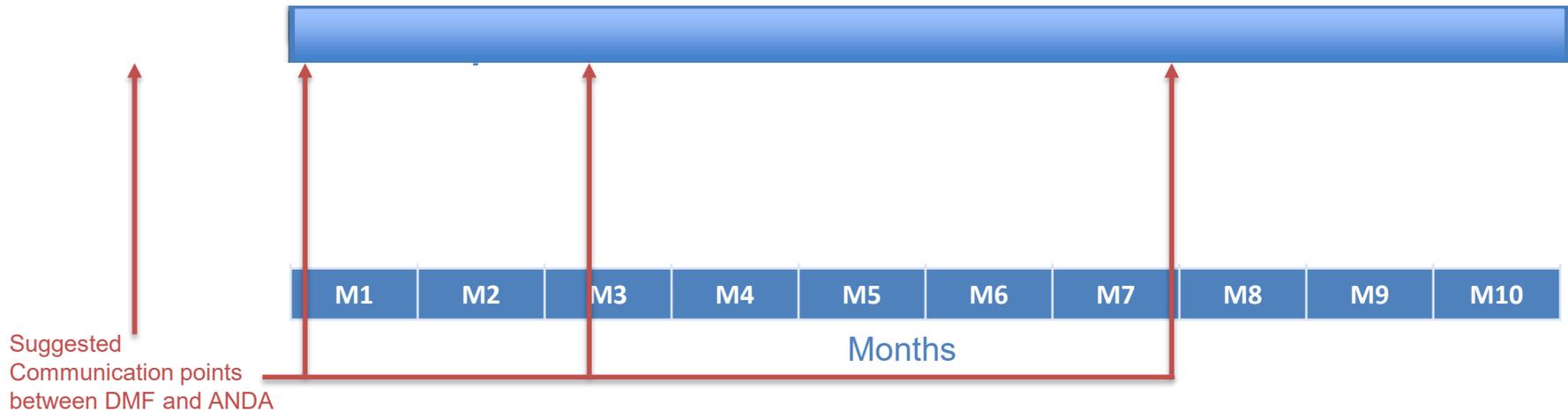


Introduction

**DMF Timeline**

Communication

Improvement Areas



Outgoing communications: FDA to ANDA, FDA to DMF

ANIMATED VERSION

Where is the DMF: With OGD With OPQ With OPQ/DMF under review With DMF holder

# Completeness Assessment (CA)

Introduction

DMF Timeline

Communication

Improvement Areas

**Commitment Letter:** “Complete the initial completeness assessment review for **90 percent of Type II API DMFs within 60 days** of the later of the date of DMF submission or DMF fee payment.”

CA Data from 10/1/2018 through 9/30/2019:

- Total CA (first cycle) Completed: 453
- Total Completed within 60-days: 421
- Total Not Completed within 60-days: 32
- Metric: **92.9%**

# Completeness Assessments - Reminder

Introduction

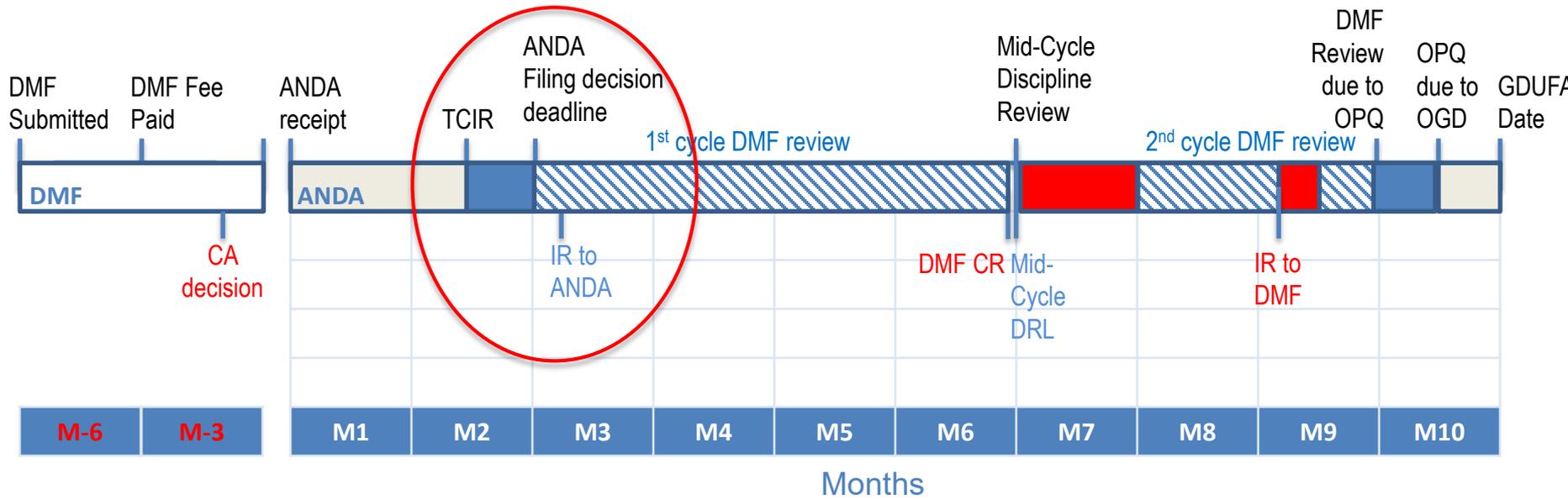
DMF Timeline

Communication

Improvement Areas

- **Observations:** No major issues with filing
- **Impact:** Refuse to Receive (RTR) for ANDA
- **Recommendation:**
  - Continue to pay the fee 3-6 months prior to ANDA submission
  - If DMF holder does not see the DMF on the *available for reference list* or does not receive an *incomplete letter* by approximately day 45 after payment, email [DMFOGD@FDA.HHS.GOV](mailto:DMFOGD@FDA.HHS.GOV) for status check
  - If DMF holder is aware that submission of a referencing application is imminent and referenced DMF is not on the available for reference list, contact [DMFOGD@FDA.HHS.GOV](mailto:DMFOGD@FDA.HHS.GOV)

# Timely Consults and Information Requests (TCIR) phase



Outgoing communications: FDA to ANDA, FDA to DMF

Where is the DMF:  With OGD  With OPQ  With OPQ/DMF under review  With DMF holder

# Timely Consults and Information Requests (TCIR)

Introduction

DMF Timeline

Communication

Improvement Areas

In an effort to improve the opportunities for first cycle approvals OPQ asked each review discipline to identify areas where early communication with the applicant could facilitate resolving issues early in the review cycle.

## Consults

Issue: Take a long time to resolve

Example: Duration of use, MDD, Impurity Qualification

## Hidden Facilities

Issue: New facilities discovered late in the ANDA review cycle do not allow sufficient time for evaluation or inspection and would prevent an approval

Example: Routine testers, multiple micronization facilities, multiple DS manufacturers (CSN)

# TCIR – Hidden Facilities

Introduction

DMF Timeline

Communication

Improvement Areas

- Looking for facility discrepancies between what the applicant lists on their 356h form for API manufacturing sites and routine release/stability testing sites and what the DMF lists for these facilities.
- Issue comments to the applicant when there are discrepancies or ambiguities in the facility information.
- DLAPI was the first OPQ discipline to implement a TCIR process (October 1, 2017).
- Since GDUFA II we have performed 1842 TCIR evaluations
- The data indicate there [are issues between the DMF holder and applicant in communicating accurate API facility information to FDA.](#)

# TCIR Results – DMF Hidden Facilities

Introduction

DMF Timeline

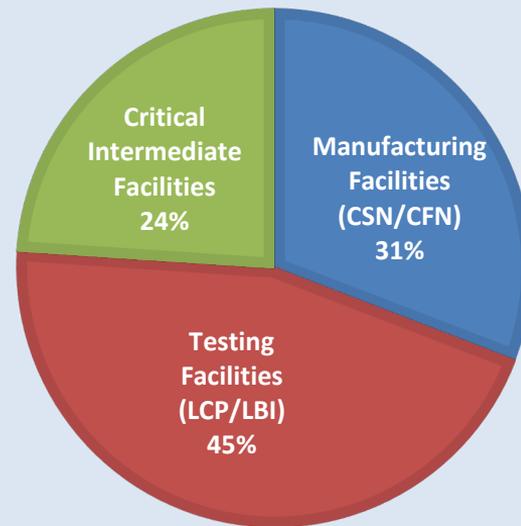
Communication Types

Improvement Areas

Description	Number
Total number of unique ANDAs evaluated	1842
Number of applications with at least one hidden facility	294
Total number of hidden facilities identified	409
Overall percentage of ANDAs with a hidden facility issue	16%

This high number is indicative of poor communication between applicants and DMF holders regarding the DMF related facilities that support their ANDAs.

## Hidden Facilities by Category



# TCIR Results – DMF Early Consults

Introduction

DMF Timeline

Communication Types

Improvement Areas

Description	Number
Total number of unique ANDAs evaluated	1842
Number of applications with at least one consult submitted	66
Total number of consults submitted	70
Overall percentage of ANDAs with early consults	3.6%

Majority of the early consults are due to Pharmacology/Toxicology consult for impurity qualification

**Consult Categories:**

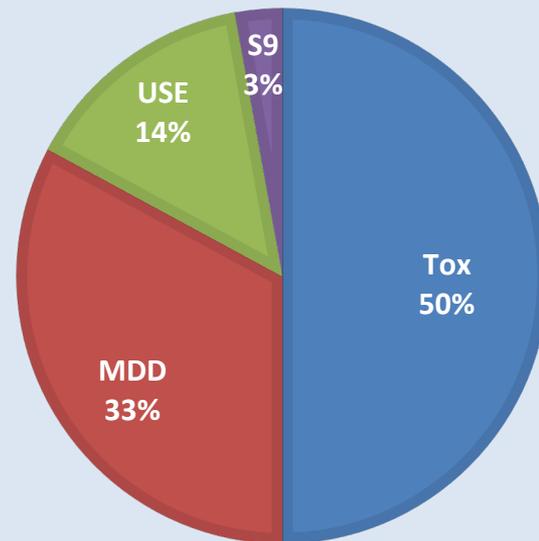
USE = Duration of use

MDD = Maximum Daily Dose

TOX = Pharmacology/Toxicology

S9 = ICH S9 Exemption

Types of Early Consults



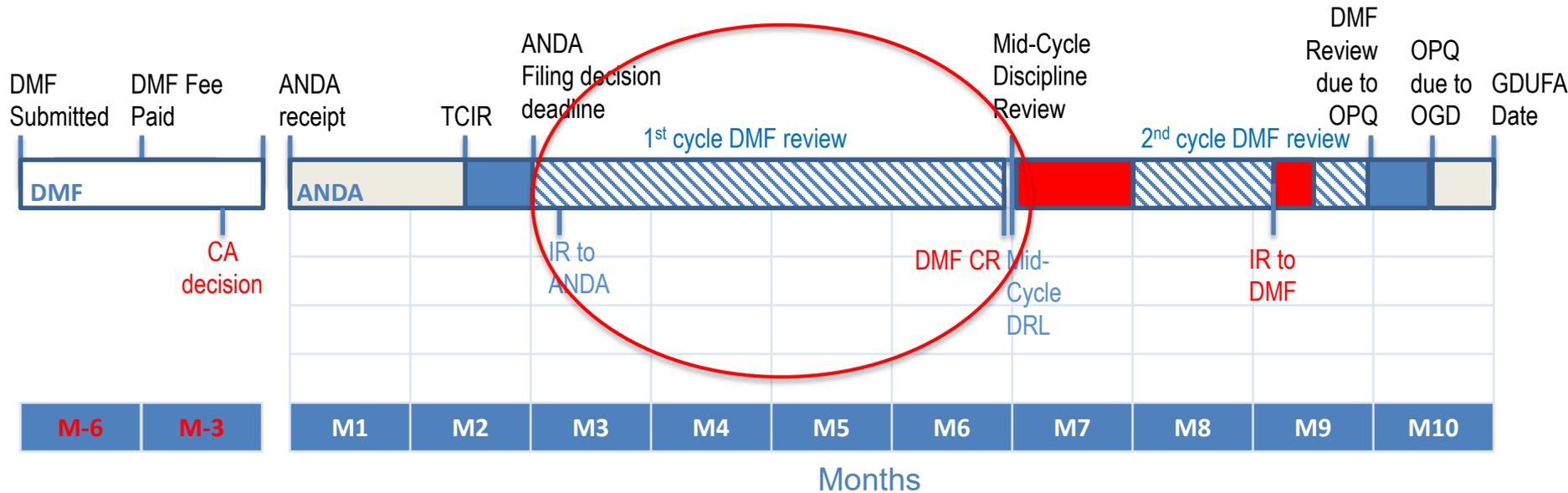
# DMF Review Phase (1<sup>st</sup> cycle, with FDA)

Introduction

DMF Timeline

Communication

Improvement Areas



Outgoing communications: FDA to ANDA, FDA to DMF

Example Timeline

Where is the DMF:  With OGD  With OPQ  With OPQ/DMF under review  With DMF holder

# “First IR Letter” for ANDA

Introduction

DMF Timeline

Communication

Improvement Areas

- For a 10-month ANDA clock the first IR letter date (also referred to as the Mid-cycle date or Discipline Review letter (DRL) date) is defined as month 5 plus 30 days (i.e. day 180).
- To meet the commitment the [DMF comments must be issued to the holder on or before this Mid-cycle date](#).
  - DMF **Information Request (IR)**: Review cycle is still ongoing for the DMF assessment
  - DMF **Complete Response (CR)**: Review cycle is closed for the DMF assessment
- The internal target for the DMF is to finish the review 3-weeks prior to the Midcycle date.
  - Allows time for the DP reviewer to update based on the DMF review
  - Allows time for the Project Managers to process the letters

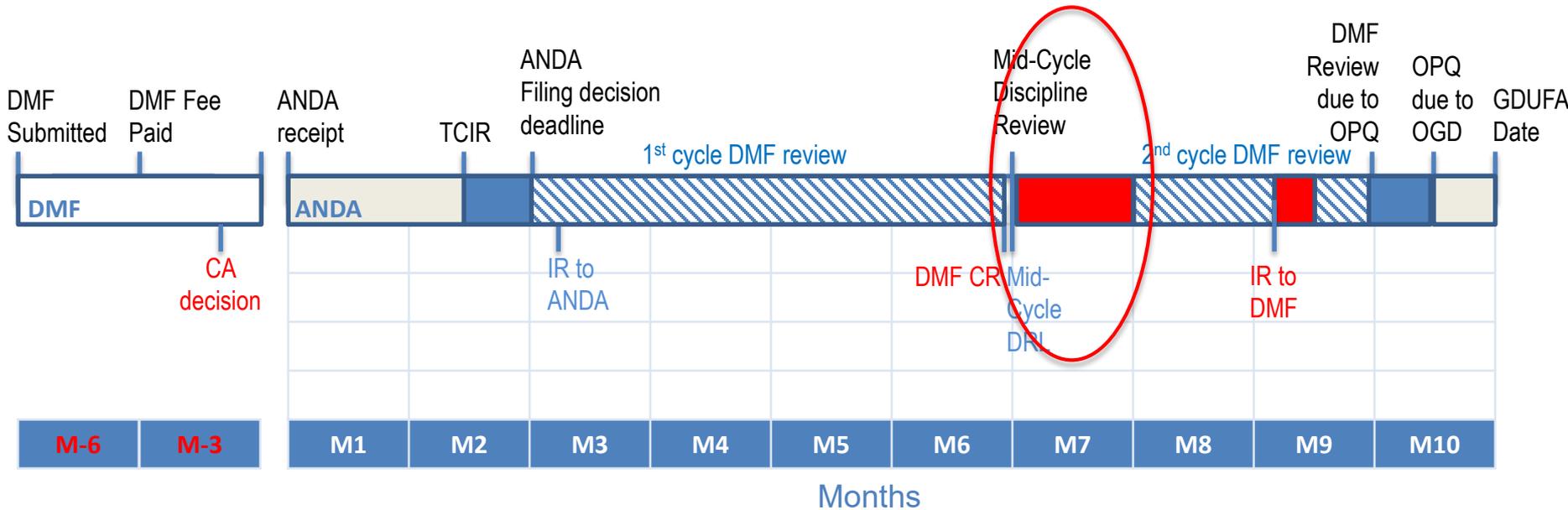
# DMF Review Phase (with DMF holder)

Introduction

DMF Timeline

Communication

Improvement Areas



Outgoing communications: FDA to ANDA, FDA to DMF

Example Timeline

Where is the DMF:  With OGD  With OPQ  With OPQ/DMF under review  With DMF holder

# Mechanism to Seek Clarification from FDA

**Commitment Letter:** FDA will grant and conduct **teleconferences** when requested to clarify deficiencies in first cycle DMF deficiency letters.

**Commitment Letter:** In lieu of a teleconference, the DMF holder may submit a request for an **email exchange** between FDA and the DMF holder. The request must identify specific issues to be addressed. After FDA responds to the request, the DMF holder may submit, and FDA will respond to, one follow up email to obtain additional clarification.

# E-mail Exchange Implementation

Introduction

DMF Timeline

Communication

Improvement Areas

- Detailed instructions are included in the DMF CR letters on how to submit
- Issue the response within 30-days of receiving the initial email exchange request
- We will respond to email exchange requests generated from any cycle (i.e. not limited to first cycle) or type of letter issued (i.e. DMF IR letter).
- We prefer to receive these requests within 20-business days but we will not deny the request if late.

# E-mail Exchange Implementation

Introduction

DMF Timeline

Communication

Improvement Areas

- In FY18 and FY19, we received and provided 118 initial email exchange responses and 13 follow-up email exchange responses.
- All have been provided within 30-days with the average response time of 16 days.
- Approximately 6.4% of letters generate a t-con or email exchange request.

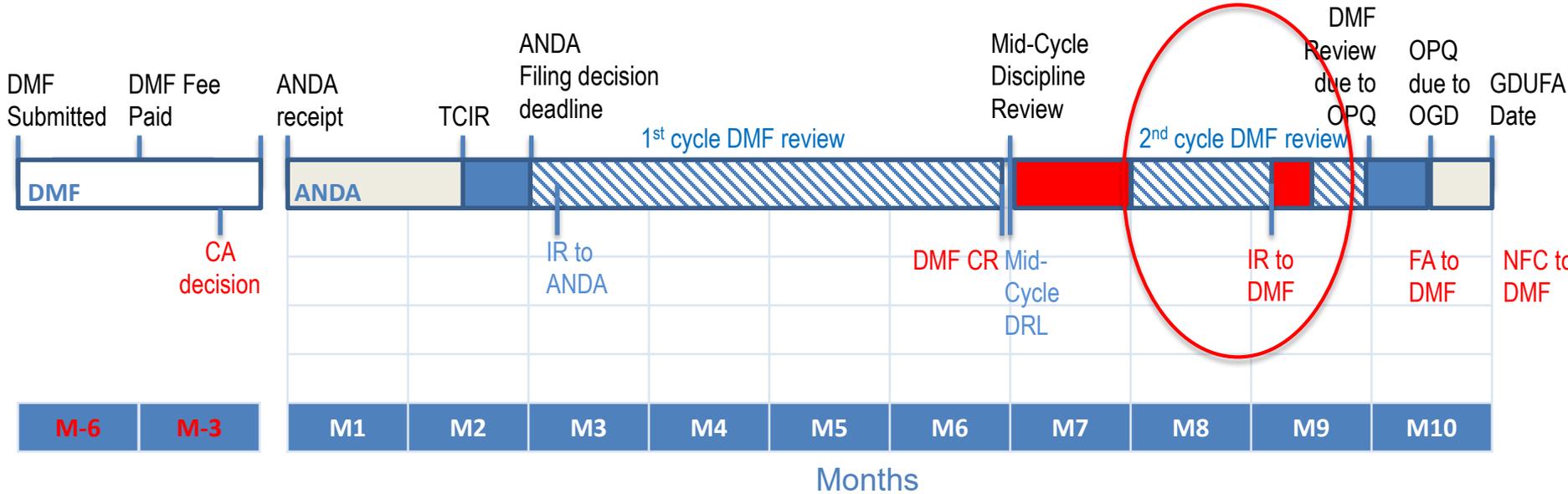
# DMF Review Phase (2<sup>nd</sup> cycle, with FDA)

Introduction

DMF Timeline

Communication

Improvement Areas



Outgoing communications: FDA to ANDA, FDA to DMF

Example Timeline

Where is the DMF:  With OGD  With OPQ  With OPQ/DMF under review  With DMF holder

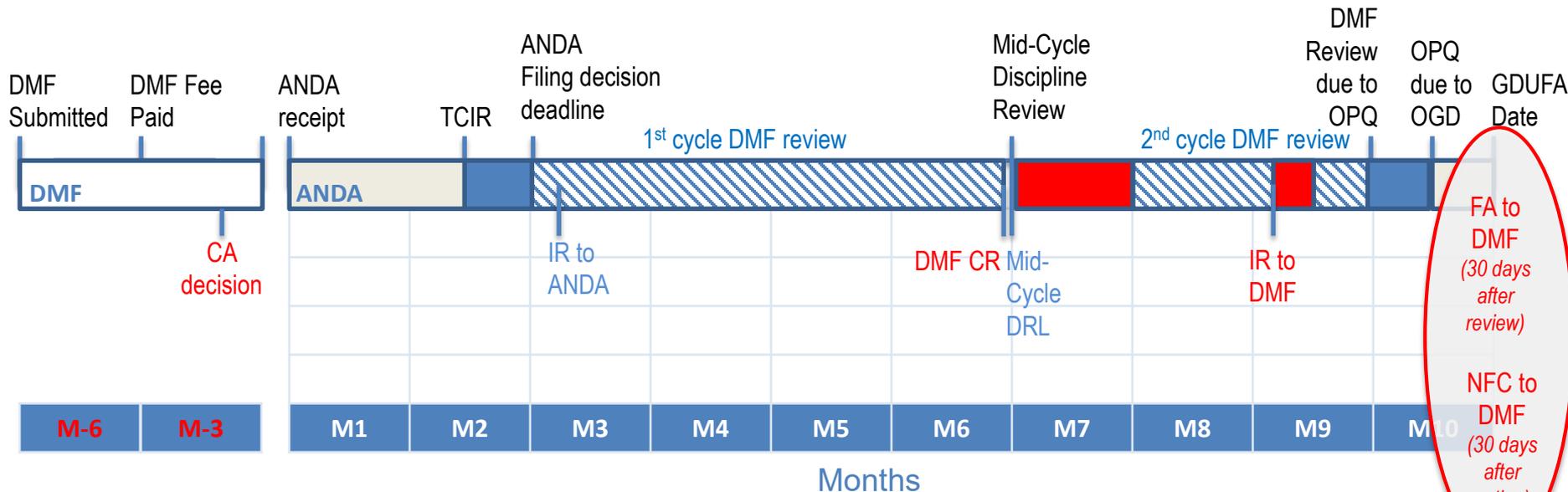
# DMF Adequate

Introduction

DMF Timeline

Communication

Improvement Areas



Outgoing communications: FDA to ANDA, FDA to DMF

Example Timeline

Where is the DMF:   With OGD   With OPQ   With OPQ/DMF under review   With DMF holder

# DMF Additional Comment (AC) Letter

Introduction

DMF Timeline

Communication: *Letter type*

Improvement Areas

- DMF Additional Comment (AC) letter
  - This was called an Information Request Letter under GDUFA I.
  - Issued to communicate very minor comments that do not make the DMF inadequate
  - Typically used when comment are minor and not enough time to resolve them by an IR.
  - Issued after ANDA action is taken to prevent late cycle amendment disrupting the ANDA review timeline
  - If multiple ANDA timelines are impacted, DLAPI tracks and issues the letter to minimize potential impact.
- Regulatory status of the DMF: Adequate and can support an approval action.
- Review status: DMF review cycle closes with an adequate recommendation.
- [We expect to get a response within 6-months of sending the letter.](#)
- DMF holder should coordinate with ANDA applicant before responding to an AC letter.

# DMF Deficiency Letter

Introduction

DMF Timeline

Communication: *Letter type*

Improvement Areas

- DMF Deficiency letter
  - Issued to communicate deficiencies in cases where the DMF CR letter does not apply
  - Issued for non-API type II (i.e. secondary DMFs for intermediates), non-type-II DMFs, DMFs referenced only by an NDA/IND
- Regulatory status of the DMF: DMF is inadequate and cannot support an approval action.
- Review status: DMF review cycle closes when the letter issues (i.e. can support a CR action on a referencing application)

# Common Barriers to ANDA Approval

Introduction

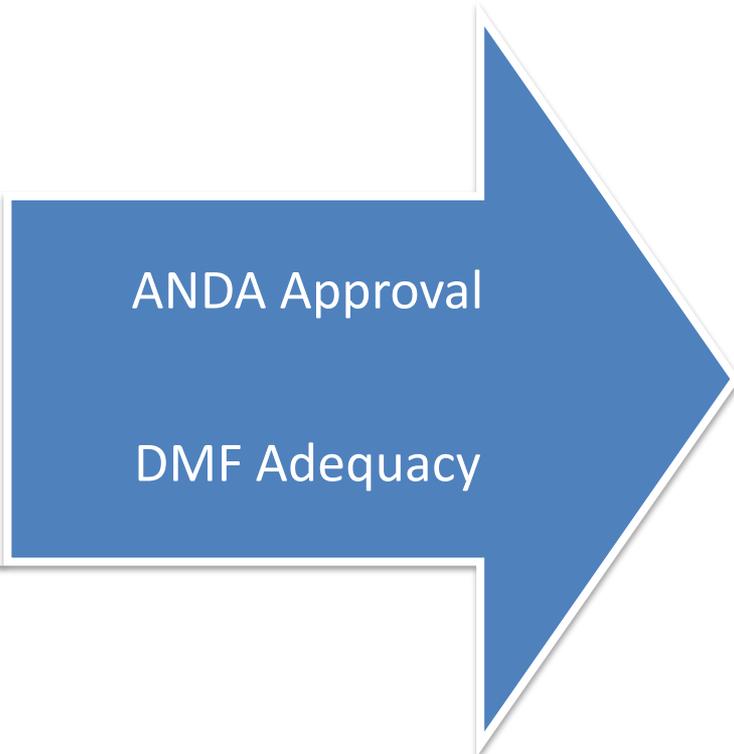
DMF Timeline

Communication

Improvement Areas



DMF Hidden Facilities  
Unsolicited Amendments  
Major Deficiencies



ANDA Approval  
DMF Adequacy

# DMF Hidden Facilities

Introduction

DMF Timeline

Communication

Improvement Areas

- **Observations:**
  - DMF facilities not communicated to ANDA holder
  - Function of the DMF facilities unclear (e.g. multiple API manufacturing sites, micronization sites, routine testing sites)
  - Improper selection of a SM resulting in reclassification of a starting material as a late stage intermediate
- **Impact:**
  - Facilities flagged for further evaluation
  - Newly classified late stage intermediate facility requires assessment late in the review cycle
  - Potential delay in application approval if inspection is needed
- **Recommendation:**
  - DMF holders need to communicate all critical DMF facilities, responsibilities of each manufacturing or testing site to the ANDA applicant early
  - DMF facilities and responsibilities should be clearly identified in 3.2.S.2 and relevant facilities included in the LOA
  - Enable early identification and inspection of facilities if required

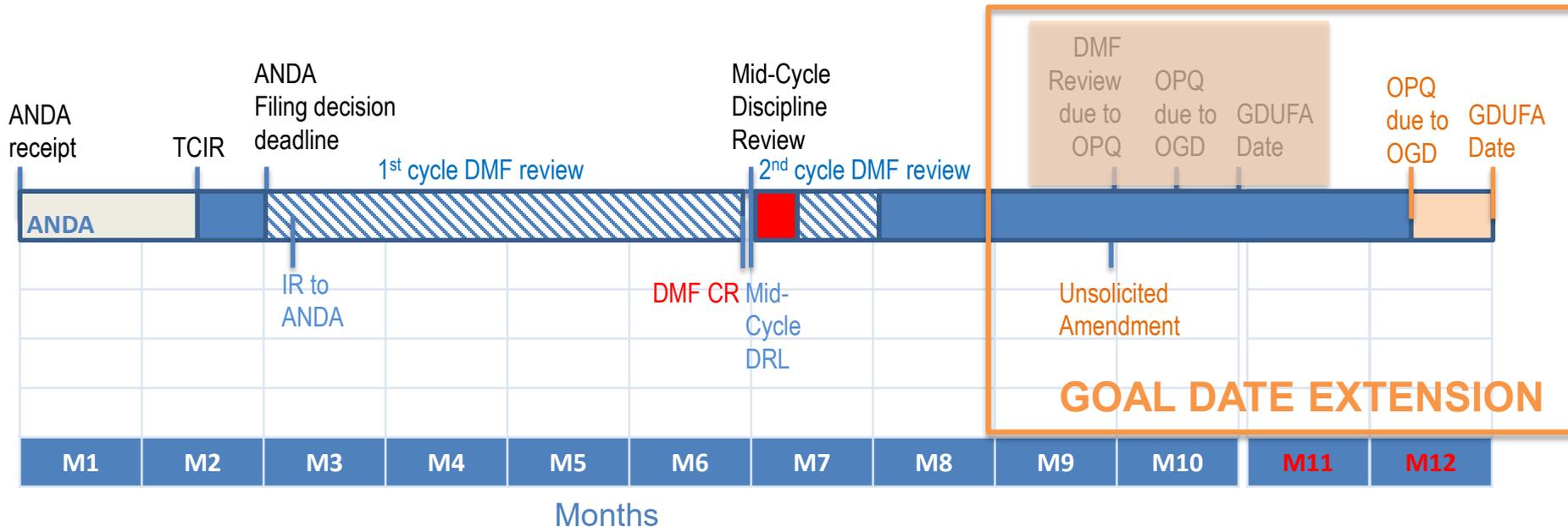
# DMF Unsolicited Amendment Example

Introduction

DMF Timeline

Communication

Improvement Areas



Outgoing communications: FDA to ANDA, FDA to DMF

ANIMATED VERSION

Where is the DMF:   With OGD   With OPQ   With OPQ/DMF under review   With DMF holder

# DMF Unsolicited Amendments

Introduction

DMF Timeline

Communication

Improvement Areas

- **Observations:**

- Unsolicited amendments to the DMF submitted in the last third of an ANDA review cycle
- Timing of DMF submissions not in sync with ANDA status and action timeline
- Unsolicited amendments often do not contain information critical to review prior to an approval for referencing ANDA

- **Impact:**

- The DMF may cause an extension of the goal date to allow sufficient time for review
- The DMF amendment may be deferred to the next review cycle and contribute to an ANDA CR

- **Recommendation:**

- Inform customers with pending ANDAs when you are going to submit a DMF amendment
- DMF holders should be aware of the status of the DMF (FA, NFC letters)
- Limit the number of unsolicited amendments by combining minor changes to decrease detrimental impact on pending ANDA action

# DMF Unsolicited Amendments – FDA Help

Introduction

DMF Timeline

Communication

Improvement Areas

- If the status of the DMF is unclear then email [DMFOGD@FDA.HHS.GOV](mailto:DMFOGD@FDA.HHS.GOV) to obtain real-time update.
- If the status and timelines for referencing applications are complicated and/or not clear then email us.
  - We have access to the current open cycles for all referencing submissions (original ANDAs, supplements, NDAs).
  - We can help you plan an optimal submission strategy to minimize impact on referencing applications
- Very basic information on the planned date of the DMF submission and the nature of the changes is all that is required.

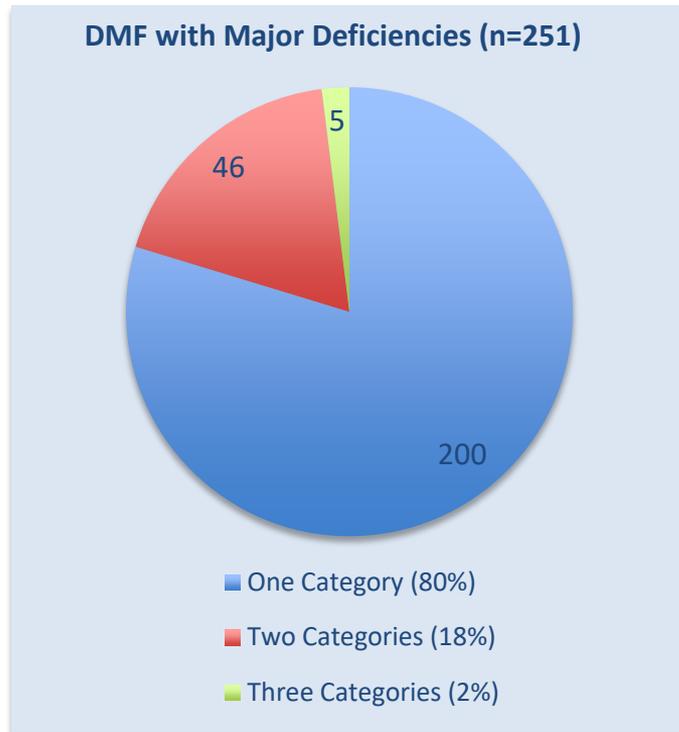
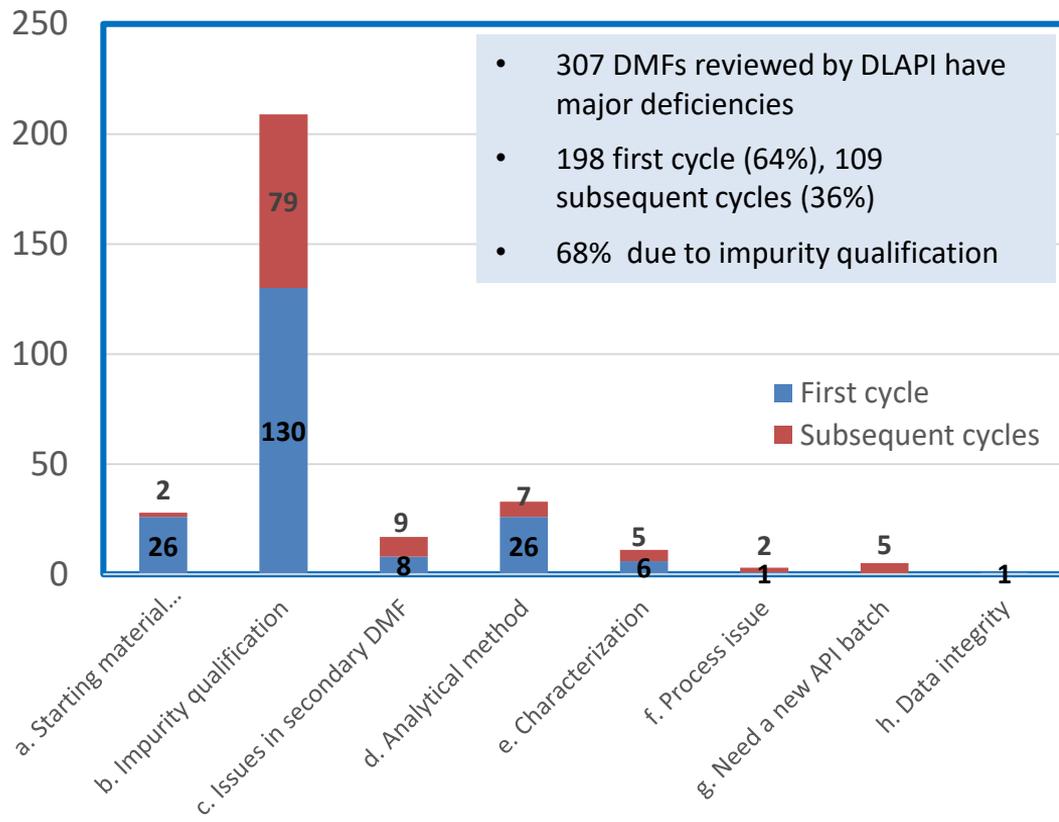
# Major DMF Deficiencies – DS Categories

Introduction

DMF Timeline

Communication

Improvement Areas



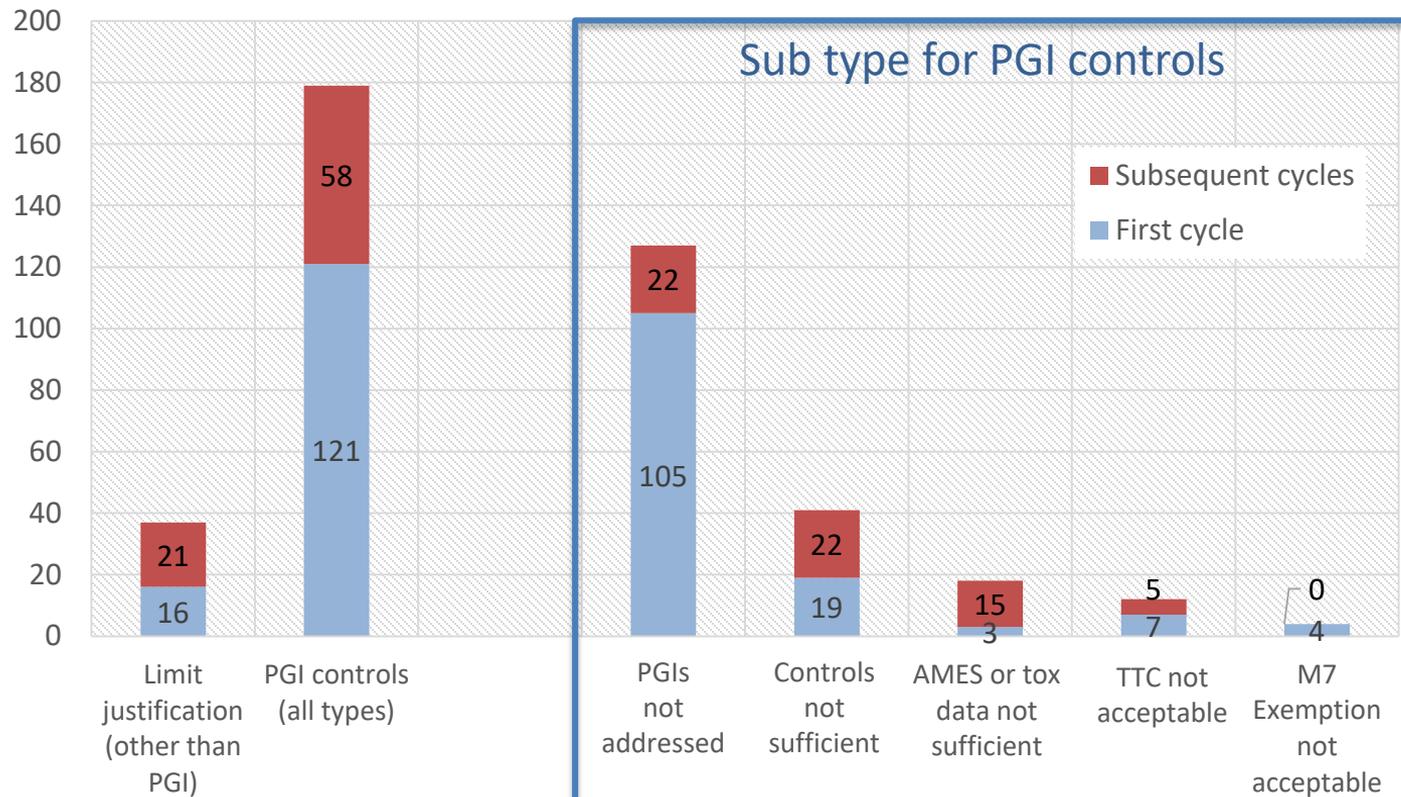
# Major DMF Deficiencies – PGI Controls

Introduction

DMF Timeline

Communication

Improvement Areas



*Potential Genotoxic Impurity (PGI) Controls are the main reason for major issues with impurity qualification (across all cycles)*

# Deficiency Response Timing

Introduction

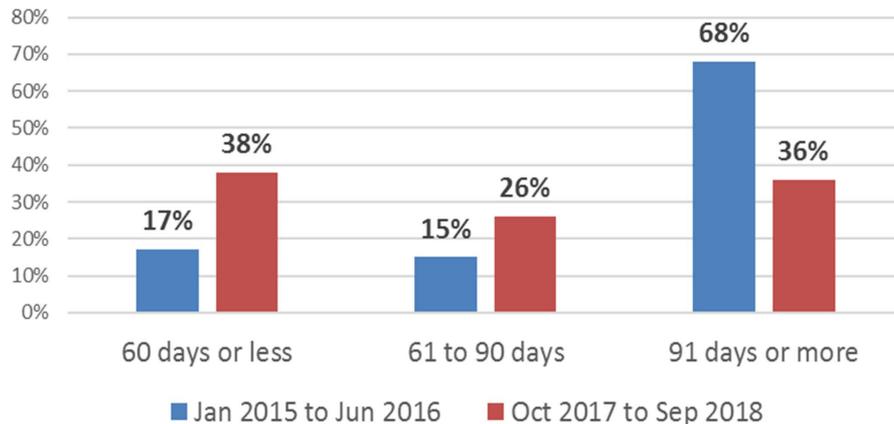
DMF Timeline

Communication

Improvement Areas

- 98% of DMFs being reviewed for the first time are found inadequate and issued a DMF CR letter.
- Most of these DMFs will receive two or three touches before becoming adequate.
- Reducing both the total number of review cycles and the time for response from the DMF holder is critical to increasing the chances for a first cycle ANDA approval.

## Response Time for First CR letter



Need to further **improve first cycle response times** to be compatible with first-cycle ANDA approvals in an 10-month or 8-month review clock.

# Administrative Reminders

Introduction

DMF Timeline

Communication

Improvement Areas

- Every submission should include an administrative information page and a cover letter.
- LOAs should be in 1.4.1 (do not have to resubmit the original letters each time) – list of authorized firms should be in 1.4.3
- Separate LOAs for each DMF and each referenced party
  - Cannot submit one LOA for multiple parties
  - Cannot submit one LOA for multiple DMFs
- DMF subject = DMF title; use consistently
- If monograph is added, just adding “USP” to the cover letter doesn’t change the title – submit an amendment
- Change to holder or facility address, must submit an amendment

# Acknowledgements

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- Dave Skanchy
- Deborah Johnson
- Ram Randad
- Jayani Perera
- Wei Liu
- Wei Song
- Keduo Qian



# **ADDITIONAL INFORMATION**

# DMF Timeline – Original/New DMF Example

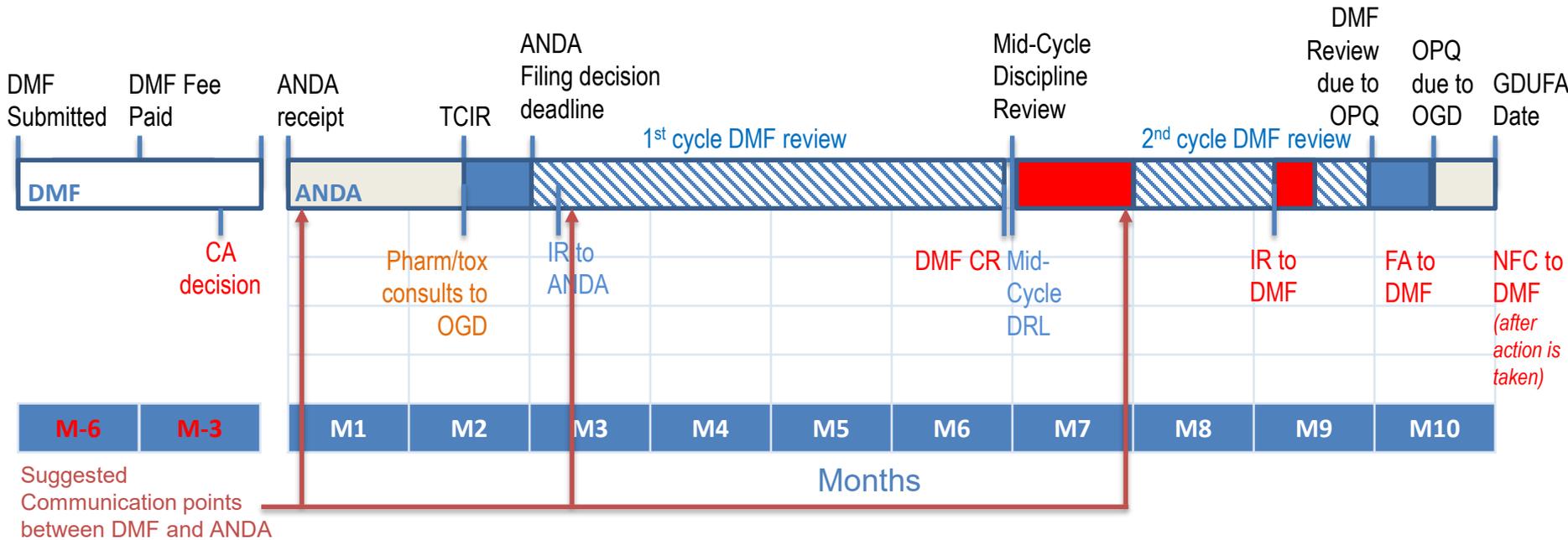


Introduction

**DMF Timeline**

Communication

Improvement Areas



Outgoing communications: FDA to ANDA, FDA to DMF

PRINT VERSION

Where is the DMF:   With OGD   With OPQ   With OPQ/DMF under review   With DMF holder

DMF holders must **request such teleconferences in writing within 20 business days** of issuance of the first cycle DMF deficiency letter, identifying **specific issues** to be addressed. FDA may initially provide a written response to the request for clarification, but if the DMF holder indicates that a teleconference is still desired, FDA will schedule the teleconference. FDA will strive to grant such teleconferences within 30 days, giving priority to DMFs based on the priority of the referencing ANDA.

# Implementation of Teleconference

Introduction

DMF Timeline

Communication

Improvement Areas

- Functions the same as under GDUFA I
- Issue a grant or deny letter for the t-con within 30-days
- May issue written comments with the grant letter – DMF holder’s option to accept the written comments
- If we deny due to failure to receive the t-con request within the 20-business days we will offer to do an email exchange or other suitable route to answer the questions.
- Since GDUFA II (FY 2018 and FY 2019), we received and granted 12 teleconference requests

# GDUFA 2 DMF Communication: Letter Types

Introduction

DMF Timeline

Communication: *Letter type*

Improvement Areas

- DMF First Adequate (FA) Letter
- DMF No Further Comments (NFC) Letter
- DMF Information Request (IR) Letter
- Additional Comments
- DMF Deficiency Letter

# DMF First Adequate (FA) Letter

Introduction

DMF Timeline

Communication: *Letter type*

Improvement Areas

**Commitment Letter:** Once a DMF has undergone a full scientific review and has no open issues related to the review of the referencing ANDA, FDA will issue a First Adequate Letter.

- Similar in format to the NFC letter under GDUFA I.
- Target to issue **within 30-days of the finalization of the review** finding the DMF adequate for the first time.
- Since GDUFA II (FY 2018 and FY 2019), we have issued 387 FA letters.

# DMF No Further Comment (NFC) Letter

**Commitment Letter:** Once a DMF has undergone a complete review and the ANDA referencing the DMF has been approved or tentatively approved, FDA will issue a no further comment letter.

- Identical to the NFC letter under GDUFA I.
- Target to issue within **30-days of approval action on the referencing ANDA.**
- Since GDUFA II (FY 2018 and FY 2019), we have issued 1776 NFC.

# DMF Information Request (IR) Letter

Introduction

DMF Timeline

Communication: *Letter type*

Improvement Areas

- DMF Information Request (IR) Letter
  - This was called an Easily Correctable Deficiency Letter under GDUFA I.
  - Issued to communicate deficiencies in cases where the holder should be able to respond quickly and get the DMF to an adequate status
  - May be issued relatively late in an ANDA review cycle
  - RBPMs set the response timeline (usually 10 to 30-days) but they have discretion
  - Can be used to meet the Mid-cycle commitment
- Regulatory status of the DMF: DMF is inadequate and cannot support an approval action until issues are resolved.
- Review status: DMF review cycle remains open and response is reviewed upon receipt.
- If an IR letter is not responded to in the requested timeframe the comments can be converted to a CR letter and the DMF review cycle closed.

- Deficiencies in the drug master files (DMF) may affect the major or minor category of ANDA amendments, which impacts an application's review goal dates.
  - Standard Major – 8 or 10 months (depending on if preapproval inspection is required)
  - Standard Minor – 3 months
- Reference: [Guidance for Industry, ANDA Submissions-Amendments to Abbreviated New Drug Applications under GDUFA](#)

# Major DMF Deficiencies in DS Explained

Introduction

DMF Timeline

Communication

Improvement Areas

1. Inadequate selection or justification of starting materials.
2. Toxicological studies are needed to qualify an unqualified impurity.
3. Reference to a secondary DMF which has not been reviewed, is currently inadequate, or requires submission of a technical dossier from a third party supplier with significant additional manufacturing information.
4. Failure to provide adequate analytical methods or method validation which would require significant new method development.
5. Insufficient physical or chemical characterization data to demonstrate structure, form, or drug substance sameness (especially for complex active pharmaceutical ingredients (APIs)) in the DMF.
6. Major change in drug substance manufacturing process with inadequate supporting data.
7. Requirement to manufacture a new API batch.
8. *Data reliability issue in the DMF or manufacturing/testing facilities.*

# Deficiency Response Timing Reminders

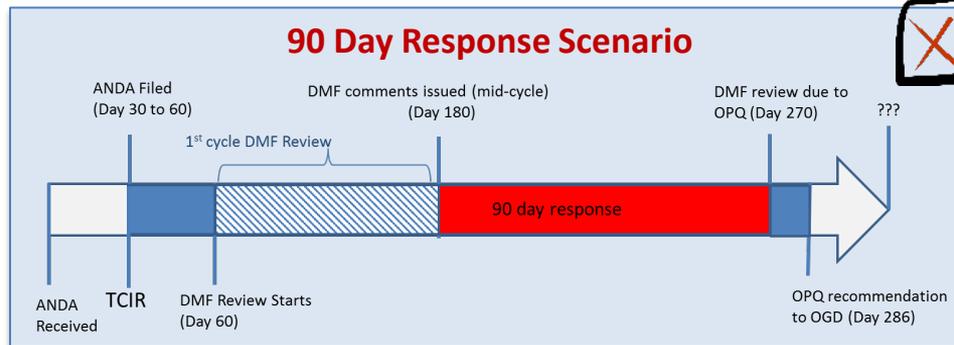
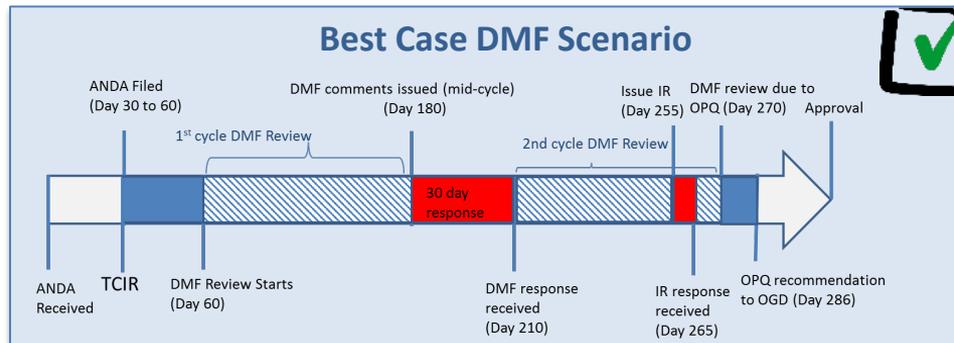
Introduction

DMF Timeline

Communication

Improvement Areas

- Respond to deficiency letters in thirty days
- Respond to Information Request (IR) letters within the requested timeframe
- Provide complete responses that address all the issues raised to reduce the need for subsequent cycles
- Use email exchanges to get clarifications quickly
- Avoid deficiencies in key areas that require a long time to respond and/or consume significant Agency resources to review



With OGD
  With OPQ
  With OPQ/DMF under review
  With DMF holder

**Commitment Letter:** By October 1, 2018, FDA will issue a guidance regarding post-approval changes to a Type II API DMF and submission mechanisms for ANDA applicants who reference the Type II API DMF.

- Draft Guidance published September 2018
- <https://www.fda.gov/media/115733/download>



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