Drug Substance Quality Assessment: Best Practices

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How to submit?

- ***ANDA or DMF (Type II MF)***
- Regulation for DMF: 21CFR314.420
- The DMF will be reviewed ONLY when it is referenced in an application or another DMF
- Not “approved”: Assessed to determine whether it is adequate to support a particular application
- Must be submitted in eCTD format after 5/5/2018

Drug substance section_CTD Format

- Module 1. Regional Admin Info
- Module 2. Quality Overall Summary (QOS)
- Module 3. Quality Information
- 3.1 Table of Contents
- 3.2 Body of Data
- **3.2.S Drug Substance**
  - 3.2.S.1 General Information
  - 3.2.S.2 Manufacture
  - 3.2.S.3 Characterization
  - 3.2.S.4 Control of Drug Substance
  - 3.2.S.5 Reference Standards or Materials
  - 3.2.S.6 Container Closure System
  - 3.2.S.7 Stability
  - 3.2.R. Regional Information

- 3.2.P Drug Product

Agency Updates to Meet Performance Goals and Program Enhancements Specified for DMFs in GDUFA II

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GDUFA User Fees

FY 2018 User Fees		
ANDA		$171,823
Annual Program	Large	$1,590,792
	Medium	$636,317
	Small	$159,079
DMF		$47,829
[1]Facility	Domestic API/	$45,367
	Domestic FDF	$211,087
	Domestic CMO	$70,362
Backlog*		$17,434
PAS		N/A

[1] Foreign Facility = +$15,000. *The one-time backlog fee was set in FY 2013 only.

Completeness Assessment Initial Review

- Agency goal is to complete 90% of DMF initial CA within 60 days of the later of the date of DMF submission or DMF fee payment

- In order to file an ANDA all Type II DMFs for the API must be “Available for Reference”
  - Pay DMF fee
  - Completeness Assessment (CA)
  - Upon “not failing” the CA, the DMF is deemed “available for reference”
  - All “available for reference” DMFs are listed on a publicly available FDA website

- Start CA process at least 6 months in advance of a referencing ANDA

- DMF should be limited to one process and one substance (different salt, different DMF)

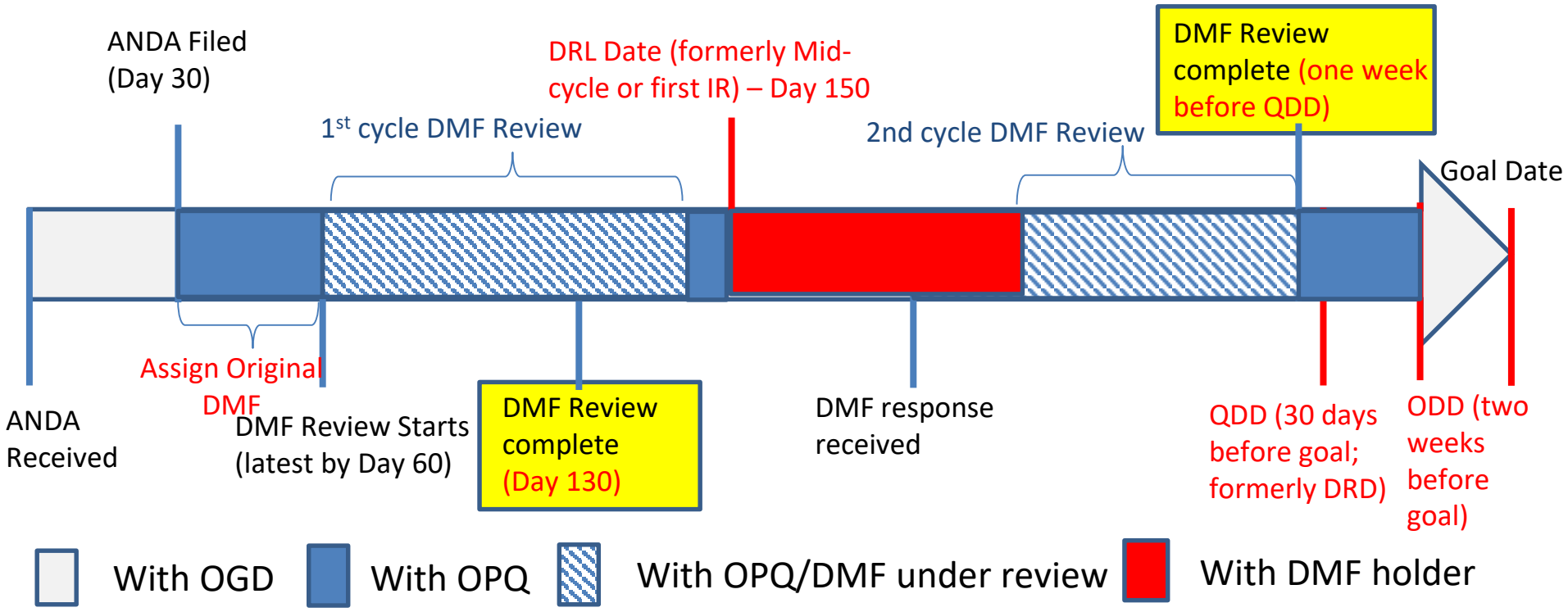
Review Program Enhancements

- Communication of DMF Review Comments
- Teleconferences & Email Exchange to Clarify DMF First Cycle Review Deficiencies
- DMF First Adequate Letters
- DMF No Further Comments Letters
- Guidance on Post-Approval Changes to Drug Substances
- Pre-ANDA program and subsequent mid-review-cycle meetings for **complex products**

Communication with DMF Holder

- DMF Review communication is aligned with ANDA
  - Applies to comments issued to the applicant in any ANDA Complete Response Letter (CRL) and comments issued in the first Information Request (IR) letter by the drug product review discipline
- Teleconference to Clarify DMF First Cycle Review Deficiencies
  - Submit a request within 20 business days from issuance of the first cycle deficiency letter
  - FDA strives to grant or deny within 30 calendar days
  - Email exchange – communicate early

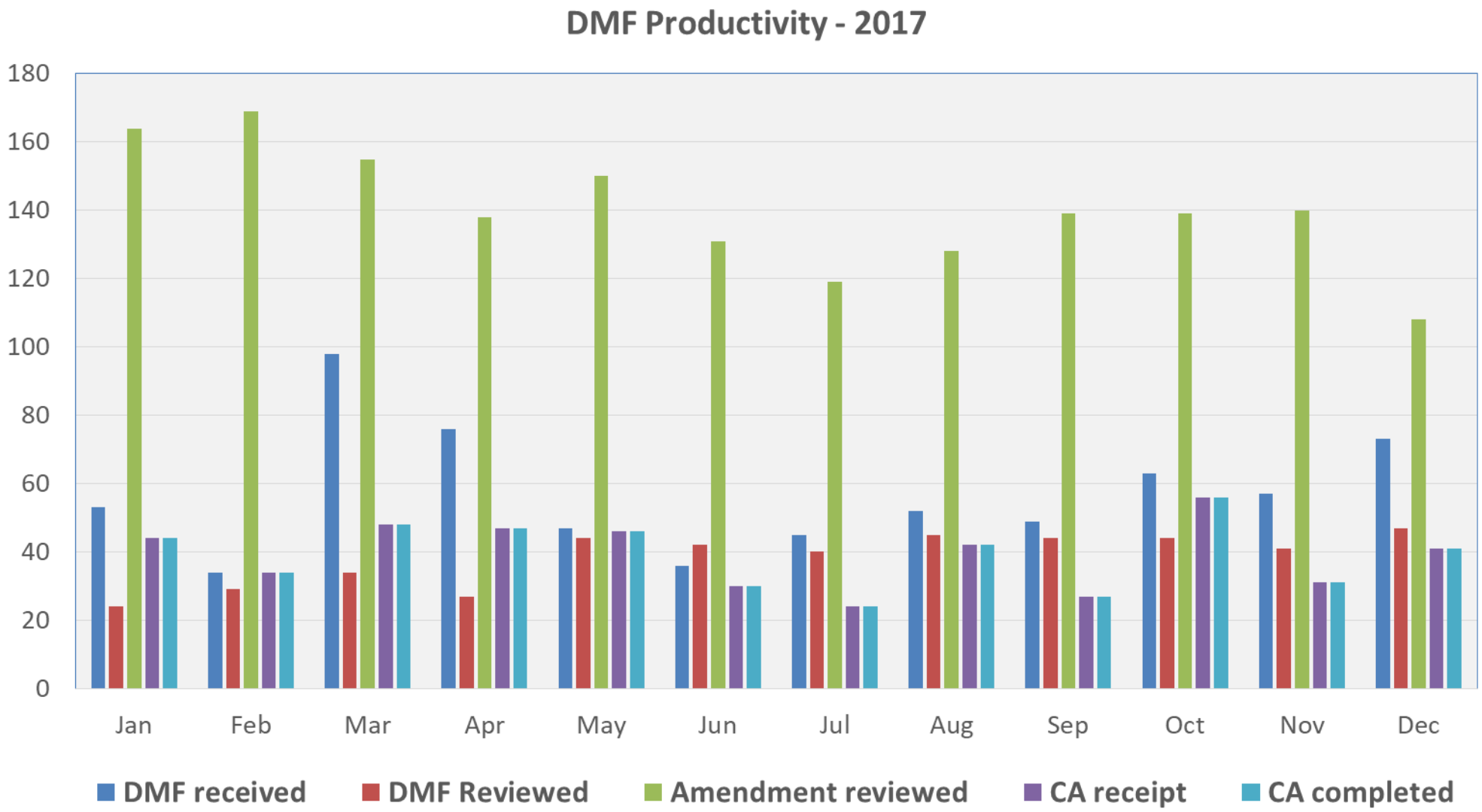
DMF Assignments Under GDUFA II



Assign Original DMFs just after filing to issue DMF CR by the ANDA mid-cycle IR date.

If the DMF holder responds in a timely way this may allow for a second cycle review before the clock runs out. **Note that we must finish before the QDD!**

DMF Productivity - 2017



What Can Industry do to Improve?

- Improve the **quality of DMF submissions** so that there are fewer deficiencies and fewer review cycles needed to get the DMF to adequate status
- **Avoid deficiencies in key areas** that require a long time to respond and/or consume significant Agency resources to review
- Applicants should clearly **communicate** the ANDA action timeline to their DMF holder (remember that the DMF is part of your application)
- Make effective use of the **T-con and email (GDUFA II)** options for getting clarification on deficiencies so responses are complete
- Respond quickly (within 10 –days) when the Agency issues an IR
- Make it your goal to respond to DMF 1st cycle letters in NMT 30 days

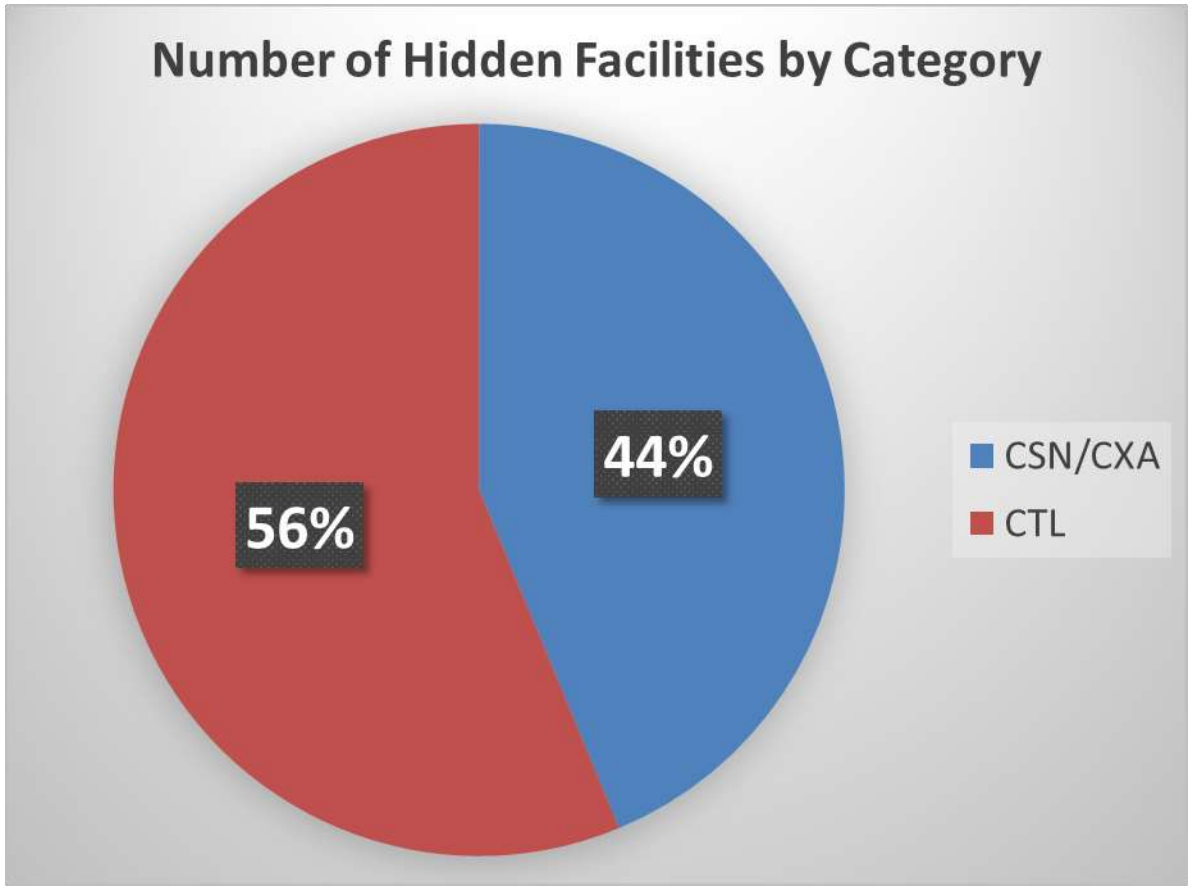
DMF Deficiencies That Impede Approval

Issues that may cause significant deficiencies in S.2

- Non-reported, **hidden facilities** (DS manufacturing site or routine release or stability testing facility): If the facility needs inspection this can take a considerable amount of time.
- **Outsourcing the majority of the manufacturing process and not providing sufficient information about it**: Lack of information about the outsourced process may generate multiple deficiencies. It also raises the risk that this facility may need inspection.
- **Multiple intermediate vendors without providing adequate data**: Reporting multiple intermediate vendors may cause deficiencies if adequate data isn't provided to show equivalent quality of material or if there are significant differences in the manufacturing processes between vendors.
- Declaring **unacceptable starting materials**: This may result in a request to move SMs back which is a significant amount of work.

Number of Hidden Facilities by Category

Facility Type	Number
CSN (Non-Sterile API by Chemical Synthesis)/ **CXA** (Plant/Animal Extraction Purified API)	35
CTL (Control Testing Laboratories)	45



DMF Deficiencies That Impede Approval

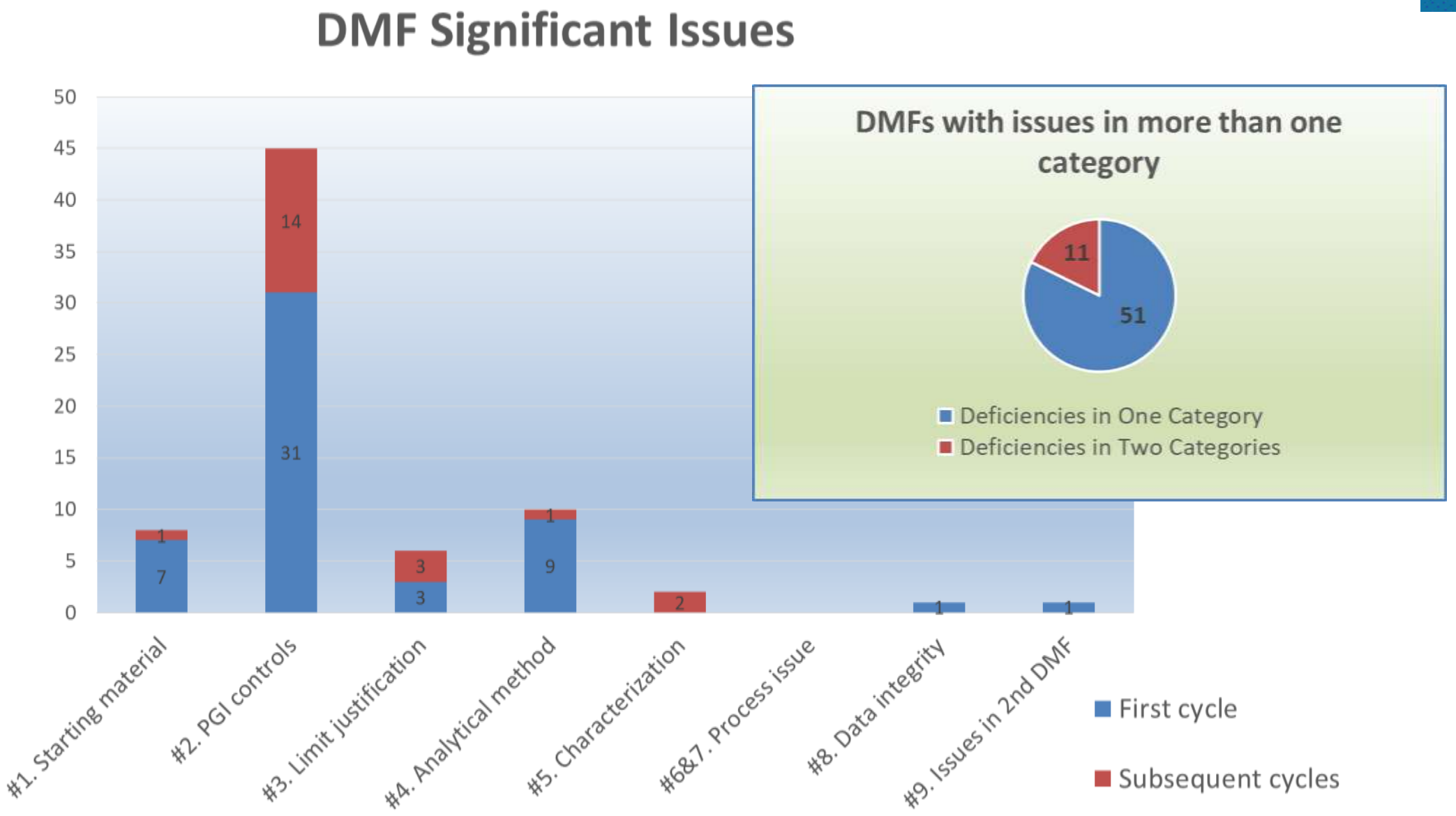
Issues that may cause significant deficiencies in S.2, cont'd

- Setting **high limits for impurities** in **IPCs and Intermediate specifications** without supporting data: This may result in the request for spike/purge studies for impurities which are not tested in the DS specification.
- **Not considering by-products** when discussing fate of residual intermediates: Discussion of the fate of materials should include data on by-products that may form due to continued reaction downstream or this may result in further questions. These requests may necessitate impurity synthesis and development of new analytical methods.
- **Not addressing impurities** such as regioisomers, stereoisomers, longer/shorter chain analogues in SM's: This may result in a request for that data. You may also discover the presence of DS analogues which are difficult to purge and which may require process modification.

Issues that may cause significant deficiencies in S.3

- Setting limits over ICH Q3A IT for regular impurities without adequate justification: Safety studies which are submitted will require a **Pharm Tox consult** which can take a significant amount of time.
- Submitting data from comparison to RLD **using only retention times**: This may result in a request for further data as HPLC RT is not a specific test for ID.

DMF with Significant Deficiencies



Potentially Genotoxic Impurity (PGI) Control

- Follow ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

Impurity Control	Data Review Timeline
CMC Options 1, 2, 3, or 4 as outlined in ICH M7, see 8.1-8.4, Tables 2, 3, 4, and Appendix 2*	With proper scale, number of batches, and spike purge, **review is immediate**
Submission of negative (Q)SAR data	Internal Consult: **2 weeks turnaround**
Submission of negative AMES data	Internal Consult: **3 months turnaround**

- *Both duration of use and maximum daily dose are critical to determination of TTC. Include discussion of these parameters in the submission

DMF Deficiencies That Impede Approval

- *Issues that may cause significant deficiencies in S.4*
  - Not submitting full **method validation** information for USP impurities when using an in-house method
  - Not submitting full **method validation** information for in-house impurities when using a USP method
  - Submitting analytical methods which lack the needed sensitivity for their intended purpose
- *Issues that may cause significant deficiencies in S.6*
  - **Changes in CCS without stability data** to support the change
- *Issues that may cause significant deficiencies in S.7*
  - Lack of **mass balance** during forced degradation studies: Raises question about whether analytical methods are stability indicating
  - **Out of Specification results in stability data** without accompanying root cause report: This will generate requests to explain OOS results

DMF First Adequate & No Further Comments Letters

- **DMF First Adequate Letter** is to inform when DMF becomes adequate for the first time and there are no open issues related to review of the referencing ANDA
  - Facilitate communication between the DMF holder and the ANDA applicant to prevent late-cycle unsolicited updates to the DMF that are disruptive to the ANDA approval process

- **DMF No Further Comments Letter** is issued once a DMF has undergone a complete review and the ANDA referencing the DMF has been approved or tentatively approved

Post-Approval Changes Guidance & Complex Products

- Draft guidance for industry will address the expectations for updates to a DMF after the DMF is found adequate

- Will include data and information submission requirements for DMF holders and referencing ANDAs

- **Complex products:** Agency will grant meetings with ANDA applicants to discuss the proposed complex product and support submission of a quality ANDA

Summary

- Most DMFs, assessed for the first time are found inadequate, will receive two or three cycles of review before becoming adequate.
- Improve the quality of DMF submissions so that there are fewer deficiencies and fewer review cycles needed to get the DMF to adequate status
- Respond to DMF 1st cycle letters in NMT 30 days and ASAP for subsequent cycles
- Take advantage of assessment program enhancements:
  - Teleconferences & email exchange and
  - Meetings for complex products

Resources

- FDA Drug Master File Page
  - https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/drugmasterfilesdmfs/default.htm
- GDUFA II Commitment Letter
  - https://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm525234.pdf
- Guidance for Completeness Assessments for Type II DMFs Under GDUFA
  - https://www.fda.gov/downloads/drugs/guidances/ucm321884.pdf
- Generic Drug User Fee Amendments Activities Page
  - https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm559570.htm
- Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA Guidance for Industry
  - https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm578366.pdf