SBIA-DMF Drug Substance Workshop

March 3 & 4, 2021 (Virtual)

Completeness Assessments (CAs): Current CA Status, KASA for CA, Common Issues & GDUFA Commitment Letter Statistics

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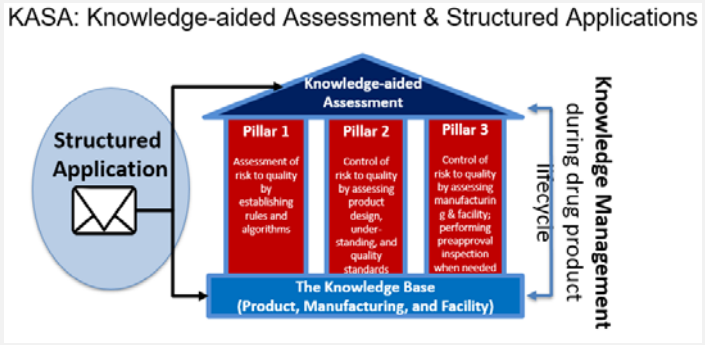
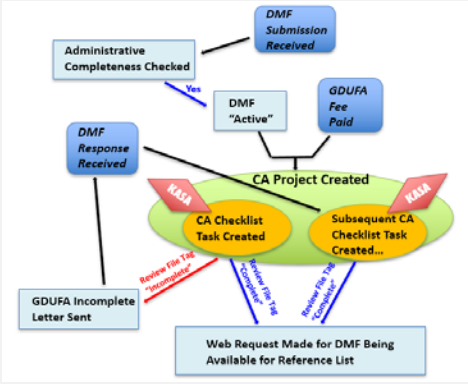
PURPOSE

This poster offers an overview of current CA and drug substance filing review [(a)2(F)] process. It is shown that exceeding of GDUFA expectation has been achieved for the CA workflow. The recent development and implementation of KASA CA interface has resulted in significant accomplishments, such as better review functions, easier data pulling, and faster process turnaround time. The observations from the CA process are used to make recommendations to industry for improving initial DMF submission quality.

METHOD(S)



KASA OVERALL STRUCTURE



CURRENT CA WORKFLOW

RESULT(S)

DATA FROM KASA

Query# of the CA Checklist	8	15	34	3	33	24	53	16	20	27
% of each for 206 CAs	21.4	12.6	12.1	10.7	8.3	7.8	7.3	5.8	5.8	5.8

HISTORICAL CA DATA

Fiscal year	GDUFA I					GDUFA II			
	FY13	FY14	FY15	FY16	FY17	FY18	FY19	FY20	FY21
%R01 Complete	23.3	43.8	45.0	53.9	66.2	50.3	43.3	51.6	54.1

OBJECTIVE(S)

1. Current Status of the CA process
2. How CA adopted the KASA process and data reporting from KASA.
3. GDUFA Commitment Letter statistics
4. Common CA issues
5. Overall advice to the industry

CONCLUSION(S)

- The implementation of KASA improved the process flow of the overall CA process.
- The Agency has met the metrics in the GDUFA II commitment letter.
- Industry has been paying fees on time and having communications with the Agency in a timely manner.
- To improve first cycle completeness of the CAs, following the CA draft guidance is suggested.

WHERE TO GET MORE INFORMATION & LINKS.

Send questions regarding this poster to: DMFWorkshop2021@fda.hhs.gov by 2/15/2021 for inclusion in the poster Q&A session on March 3rd.

Completeness Assessments for Type II API DMFs Under GDUFA Guidance for Industry:

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

Completeness Assessments (CAs)

Current CA Status, KASA for CA, Common Issues &
GDUFA Commitment Letter Statistics

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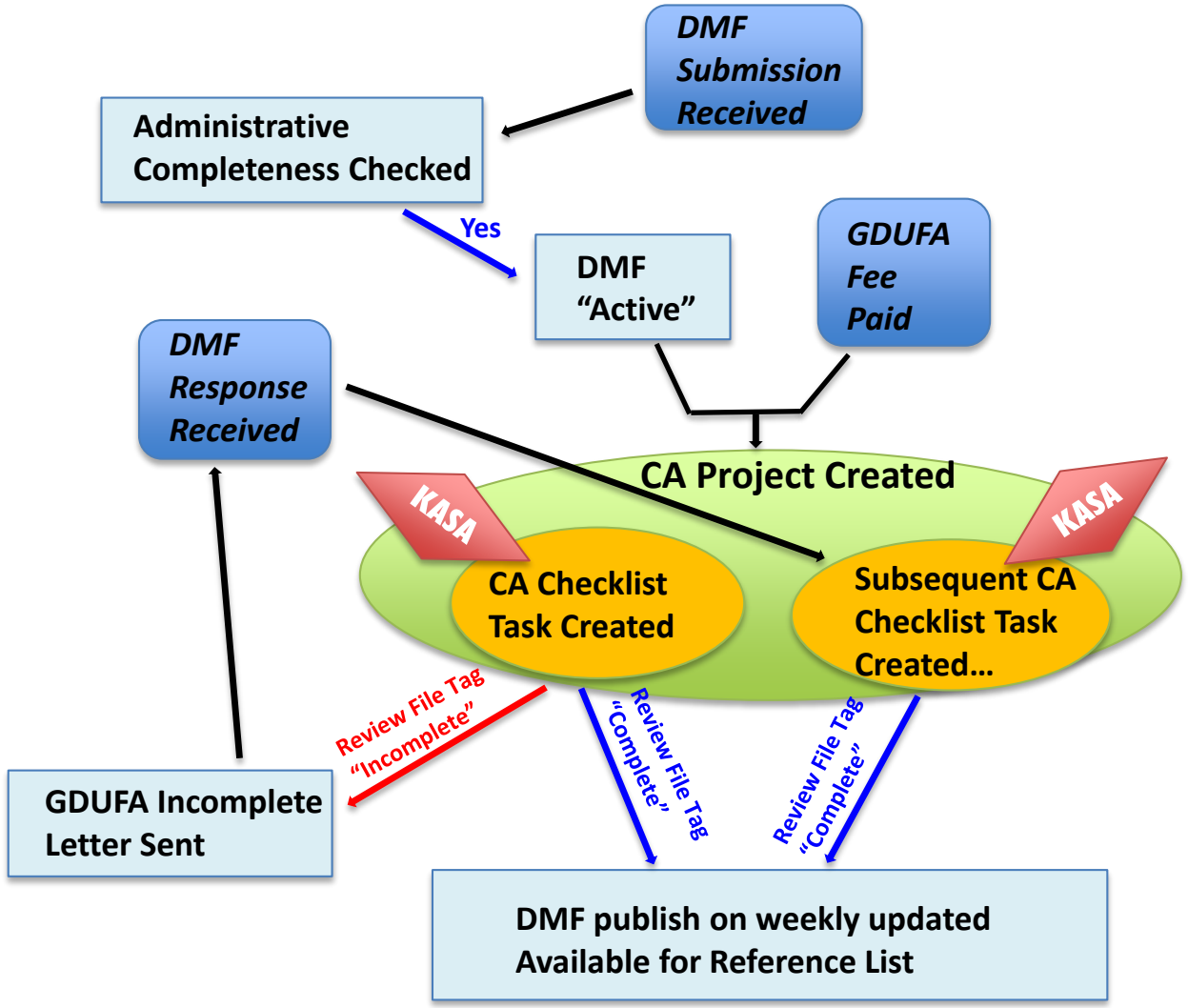
Current CA Process Flow

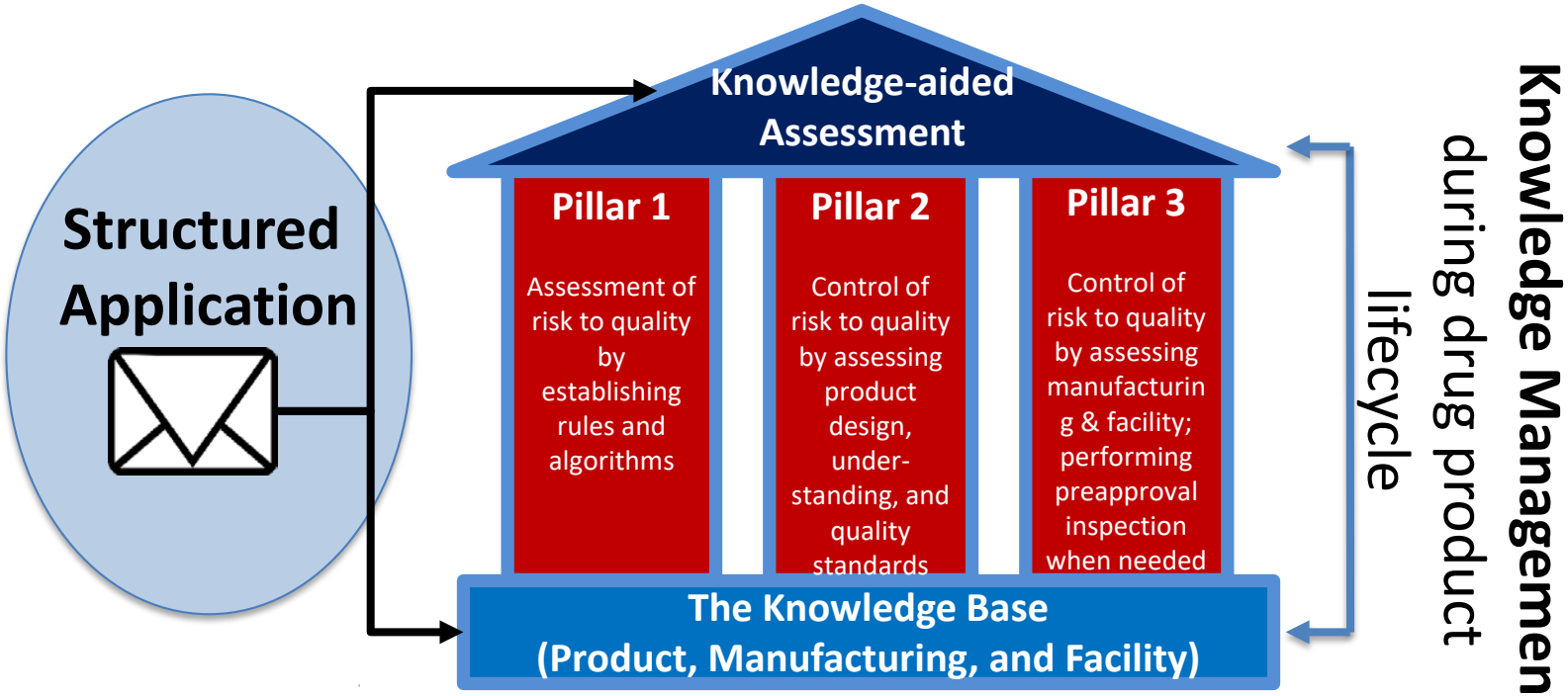


- **CA Metric:** 60 days
- **Internal Review Target:** 45 days
- **Inquiries from DMF holder/ agent Encouraged**

  (email to DMFOGD Mailbox)

KASA System

(KASA: Knowledge-aided Assessment & Structured Applications)



For more information, please see the paper:

"FDA's new pharmaceutical quality initiative: Knowledge-aided assessment & structured applications"
Lawrence X. Yu, Andre Raw, Larisa Wu, Christina Capacci-Daniel, Ying Zhang, Susan Rosencrance
International Journal of Pharmaceutics: X 1 (2019) 100010 Page 1-4

KASA CA

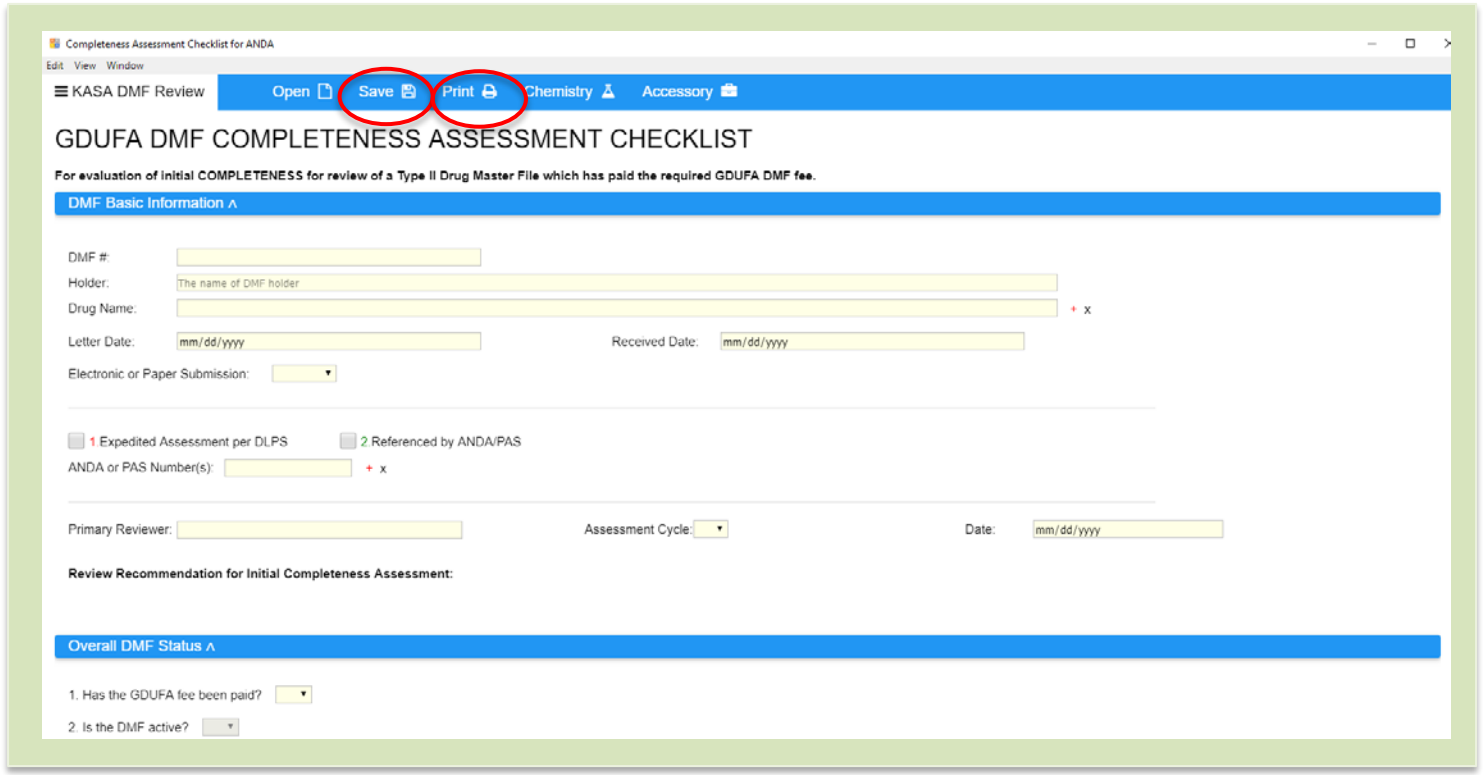
- Overall design:
  Mapping KASA for drug substance into the CDER IT supported platform

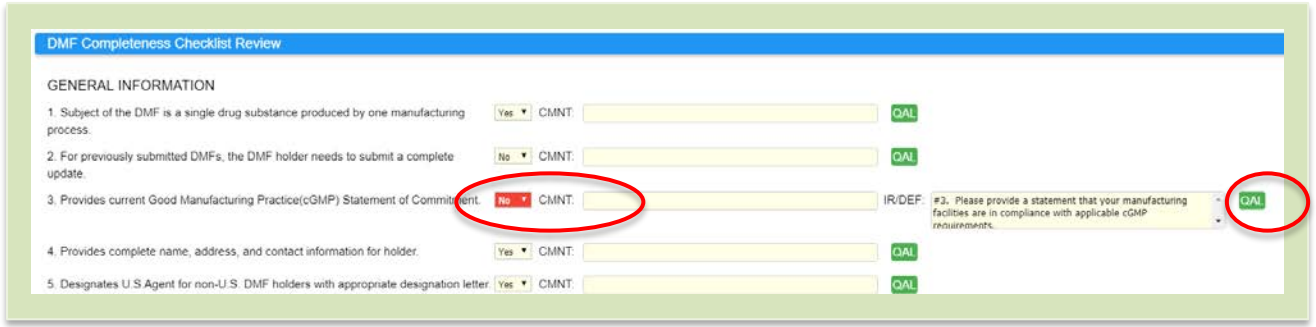
- Milestones of the project:
  - Initiative launched in December 2019
  - Beta-testing completed in March 2020
  - Fully implemented at the end of March 2020

- Performance observation:
  - Maintain the efficiency and consistency of CAs
  - Enable knowledge management
  - Provide better data reporting and data mining options

Further development:
  Alternative interface is under evaluation

KASA CA Interface





Data from KASA

- Total number of CAs completed in KASA = 206
- R01 with status “Complete” = 108
- R01 with status “Incomplete” = 98
- Find the % of appearance of each deficiency
  - ➢% of Top 10 deficiencies

Query# of the CA Checklist	8	15	34	3	33	24	53	16	20	27
% of each for 206 CAs	21.4	12.6	12.1	10.7	8.3	7.8	7.3	5.8	5.8	5.8

Top 10 Common CA Deficiencies

Query #	Subject	Examples of Common Issues
8	Label	Numerical storage temperature, Caution statement
15	General Properties	hygroscopicity, melting range, optical rotation
34	Basic Characterization	UV, EA
3	cGMP Statement	intermediate facilities, contracted labs
33	Manufacturing Process Development Summary	Not provided
24	Vendor COA for SMs	multiple SM suppliers
53	Stability Data	only initial data point
16	Manufacturing Facility Info	on-site contact person info
20	SM Designation	penultimate of API, or late-stage intermediate
27	COAs for Raw Materials	Not provided for some raw materials

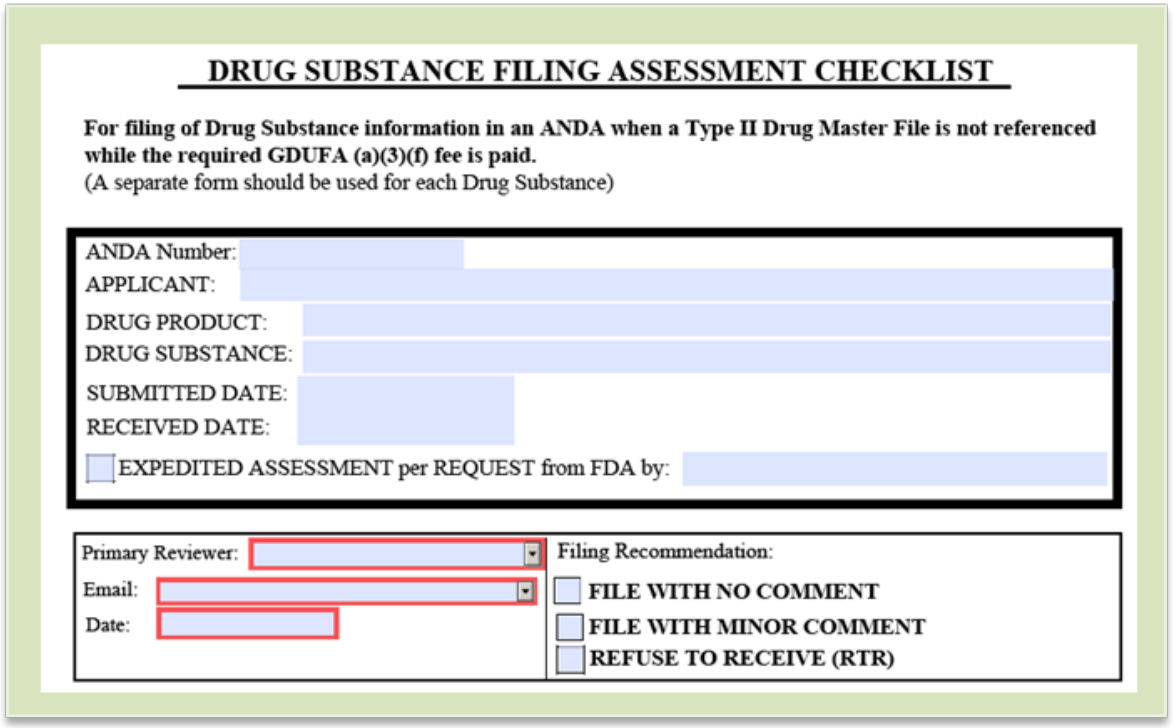
a(2)(f) Filing Review Process when DS Information is in the Application

- Applicable when there is no reference to a Type II DMF in the 356h of an ANDA Submission
- Current process involves creating a consult task by Division of Filing Review (DFR) to Division of Lifecyle API (DLAPI)
- Once the drug substance assessment is completed by DLAPI, the ANDA filing reviewer is notified

a(2)(f) Filing Review Process Cont.

- A CA-type checklist is used
- Subsequent review cycle is not commonly needed
- The a(2)(f) filing review process is not under KASA interface yet
- Major DS filing issues may result in a Refuse to Receive (RTR) of the referencing application
- Completed within the filing review timeframe usually between 30 to 60 days after the ANDA is submitted

a(2)(f) Filing Review Process Cont.



DRUG SUBSTANCE FILING ASSESSMENT CHECKLIST

For filing of Drug Substance information in an ANDA when a Type II Drug Master File is not referenced while the required GDUFA (a)(3)(f) fee is paid.
(A separate form should be used for each Drug Substance)

ANDA Number:
APPLICANT:
DRUG PRODUCT:
DRUG SUBSTANCE:
SUBMITTED DATE:
RECEIVED DATE:
☐ EXPEDITED ASSESSMENT per REQUEST from FDA by:

Primary Reviewer:
Email:
Date:

Filing Recommendation:
☐ FILE WITH NO COMMENT
☐ FILE WITH MINOR COMMENT
☐ REFUSE TO RECEIVE (RTR)

Historical Data

Calendar Year	2013	2014	2015	2016	2017	2018	2019	2020
#of a(2)(f)s	12	16	15	2	2	12	11	5

Historical CA Data

GDUFA I

	FY 13	FY 14	FY 15	FY 16	FY 17
Total #of DMFs Completed	1780	802	714	531	458
Total Full CAs	938	550	546	449	388
R01 with status “Complete”	219	241	246	242	257
%R01 Complete	23.3	43.8	45.0	53.9	66.2

GDUFA II

	FY18	FY19	FY20	FY21 (thru 01/22/2021)
Total #of DMFs Completed	384	454	303	142
Total Full CAs	326	397	244	122
R01 with status “Complete”	164	172	126	66
%R01 Complete	50.3	43.3	61.1	59.8

GDUFA II Data for Subsequent Cycle

	FY18	FY19	FY20
Total Full CAs	326	397	244
R01 with status "Complete"	164	172	126
R02 with status "Complete"	150	207	103
%R01 +R02 with status "Complete"	96.3	95.5	93.9

- The average first cycle completes are around 52%.
- Over 93% are found complete after two cycles.

RTR due to DMF

Number of ANDAs Refuse to Received (RTR) due to DMF

Fiscal Year	FY15	FY 16	FY 17	FY 18	FY 19	FY 20
ANDA RTR'd	14	11	6	4	2	1

- Completeness Assessments are rarely a filing issue

GDUFA II Commitments

- 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.

	FY 18	FY 19	FY 20
DMF Submissions	384	454	303
Met Goal	364	422	300
Metric	94.8%	93.0%	99.0%

GDUFA II Commitments

- **DMF First Adequate Letters**: 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.
- **No Further Comments Letters**: 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 Comments Letter.

	FY 18	FY 19	FY 20
First Adequate Letter	189	198	213
No Further Comments Letter	974	800	1335

What has Industry been doing well

- Pay the GDUFA fee at least 6 months prior to ANDA or PAS submission
- Submit substantially complete DMFs which not require multiple CA cycles
- Respond to incomplete letters in a timely manner
- Notify DMFOGD mailbox as instructed in the letter when submitting the response

What can Industry do to Further Improve

- To reduce the number of incomplete comments, follow the CA guidance for the type of information needs to be included in the DMF
- If you don’t hear from us within 45 days of paying the fee, email DMFOGD mailbox
- If you have submitted a DMF in paper format, please consider submitting a complete update in electronic format

Resources/helpful links

DMF Website:

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

Completeness Assessments for Type II API DMFs Under GDUFA Guidance for Industry:

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

DMF Questions:

DMFOGD@fda.hhs.gov

dmfquestion@fda.hhs.gov

CDERCollections@fda.hhs.gov

esub@fda.hhs.gov

Thank You!

- Send questions regarding this poster to: DMFWorkshop2021@fda.hhs.gov by 2/15/2021 for inclusion in the poster Q&A session on March 3rd.
- Follow-on webinar for both posters/presentations on April 9, 2021. Questions can be sent to the above email by 3/19/2021 for the webinar.
- Please refer to the following posters for cross-referenced materials:

"Teleconference" by Benjamin Danso and Jayani Perera

- Please refer to the following presentations on March 3rd and 4th for additional information:

"Modernizing Drug Substance Assessment through KASA" by Larisa Wu

"Fee payments associated with APIs – DMF/Facilities" by Evelyn Hong and Hanah Pham

" Effective Communication Strategies For Drug Master Files (DMF)" by David Skanchy and Benjamin Danso