

Poster#1: Timeline for DMF Risk-based Assessment



Presenter: Wei Song

Topic: Review timeline

Question #1:

What is the tentative time line for receiving the “No further comments letter” from receipt of First adequate letter?

Answer:

There is no timeline between receiving the “No further comments letter (NFC)” and receiving the “First adequate letter (FA)”. The mechanism for issuing these two letters is different. The purpose of sending the “First adequate letter” is to notify the DMF holder that the drug substance is found adequate to support the referenced application(s). It is triggered when the DMF review is finalized and typically issued within 30 days of the final DMF review. The NFC letter is triggered by the approval action on the referencing application. Our target is to issue this NFC letter within 30 days of the approval.

Poster#1: Timeline for DMF Risk-based Assessment



Presenter: Wei Song

Topic: Review timeline

Question #2:

Can the DMF Risk-based Assessment be initiated before an ANDA is filed after the DMF fee is paid? This may help in time saving and meeting timeline.

Answer:

While we believe that starting the DMF review earlier would be a benefit to the application review process, at present the FDA does not have the resources to initiate reviews of Drug Master Files without a filed referencing application submission. Quite simply, we cannot expend resources reviewing DMFs not associated with goal dates at the expense of DMFs that are associated with open applications with goal dates.



Poster#2: Completeness Assessments (CAs): Current CA Status, KASA for CA, Common Issues & GDUFA Commitment Letter Statistics

Presenter: Jayani Perera

Topic: Completeness Assessments

Question: Though guidelines are available on DMF and respective filing of ANDA, I would like to understand whether the ANDA applicant can file the ANDA before having the DMF Completeness assessment (CA). Can we file DMF (with data and fees) and ANDA (with data and fees) in parallel? Or should we wait for CA and then file the ANDA?

Answer:

- GDUFA does allow for the submission of the DMF and payment of the DMF fee in parallel with the submission of the referencing application
- The ANDA cannot be filed until it passes the CA and meets the “Available for Reference” requirement
- This is not the recommended approach since it places the application at high risk for a “Refuse to Receive” action
- FDA strongly encourages the DMF holder to submit a complete DMF and pay the DMF fee at least 6 months prior to application submission
- This allows for multiple cycles of CA if needed and greatly reduces the chances of an RTR

%Complete After One and Two Cycles

	FY18	FY19	FY20
Total #of DMFs Completed	384	454	303
Total Full CAs	326	397	244
R01 with status "Complete"	164	172	126
%R01 Complete	50.3	43.3	61.1
R01 with status "Complete"	150	207	103
%R01 +R02 with status "Complete"	96.3	95.5	93.9

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



Poster#3: DMF Assessments Productivity, Output, and Metrics

Presenter: Steven Kinsley

Topic: Metrics/1st cycle approvals

Question: What are the most common reasons for the low (4%) adequate rate for first-cycle reviews of original DMFs?

Answer:

- There are several reasons for the adequacy rate for first cycle reviews of original DMFs
- In regard to deficiencies, 80% of the major deficiencies are associated with impurity controls and qualifications (ICH Q3A, Q3C and ICH M7).
- Other common reasons for first cycle inadequacy include selection of starting materials (ICH Q11), and incomplete validation of analytical techniques (ICH Q2, USP<621>).
- Please refer to the following Presentations for a more detail descriptions of the types of issues leading to first cycle inadequacy: “Common CMC Issues in Type II DMFs and How to Avoid Them” and “Major Deficiencies and Facility Issues in Type II DMF”

Poster#4: Introduction to FDA Drug Master File Form 3938



Presenter: CDR David Skanchy

Topic: Facility information

Question: In the example FDA Drug Master File Form 3938 asks that every establishment related to the DMF confirm whether or not they are ready to be inspected by FDA. While this question appears to be applicable for Type II Master Files where facilities must also have Drug Establishment Registrations, it does not appear to be applicable for Type III, IV and possibly V master files. If the facility does not have an applicable FDA registration such as drug establishment, BTA, medical device registration, etc., how should they respond to the question of whether or not their facility is ready for FDA inspection?

Answer:



- In order to complete and sign the form the FEI# fields and Inspection readiness fields must be completed if an establishment is entered.
- If the facility does not have an FEI# the submitter must enter ten 9's in that field which will allow the form to be finalized
- The submitter must also indicate the facility readiness for inspection by checking the appropriate "Yes" or "No" box and filling in the date field when applicable.
- Instructions for Field 9 do include directions to specifically **not** enter facilities for packaging materials (unless a sterile process is involved) or excipients.

Poster#4: Introduction to FDA Drug Master File Form 3938



Presenter: CDR David Skanchy

Topic: Field 10: Referenced DMFs

Question: Should we contain cross referenced DMF information consistently through all DMF submissions? Is it also true in annual reports?

Answer: Yes, the current information on cross-referenced DMFs should be included on the form for each submission, including Annual Report submissions.

Poster#4: Introduction to FDA Drug Master File Form 3938



Presenter: CDR David Skanchy

Topic: Field 7: Submission Type

Question: Can I select submission type Annual report and also select Letter of Authorization?

Answer: Yes, it is a common submission scenario to submit Annual Reports with Letters of Authorization and the form will allow both submission types to be selected simultaneously when this occurs.

Poster#4: Introduction to FDA Drug Master File Form 3938



Presenter: CDR David Skanchy

Topic: Required use of DMF Form 3938

Question: Will FDA advise in advance to all DMF Holders and US Agents about when Form 3938 is mandatory ? Or, should they frequently check with DMF Website by themselves ?

Answer: FDA will post the final form and instructions when they are available for use and folks should continue to check the FDA DMF Website regularly. It is not our intent to reject submissions not including the form until industry has had sufficient time to adapt to the new form. FDA will provide ample notification as to the timing of when the form becomes a required element of DMF submissions.

Poster#4: Introduction to FDA Drug Master File Form 3938



Presenter: CDR David Skanchy

Topic: Location of the form in eCTD

Question: Which section in eCTD should Form 3938 be contained ? Is it Section 1.2 Cover letters ?

Answer: The form should be located in Module 1, under section 1.1“Forms”. Since there are no required fillable forms associated with DMFs this section is not typically used but is routinely populated with required forms, such as the 356h, in application submissions.

Poster#4: Introduction to FDA Drug Master File Form 3938



Presenter: CDR David Skanchy

Topic: Facilities

Question: Should all the outside testing facilities used for testing of the drug substance be listed in the form 3938?

Answer: The form should list manufacturing facilities and testing facilities that perform release and stability testing. Facilities that perform non-routine characterization or other studies should not be listed on the form and just listed in section 3.2.S.2.1.

Poster#4: Introduction to FDA Drug Master File Form 3938



Presenter: CDR David Skanchy

Topic: Facilities

Question: Since the form now captures the DMF facility information can the facility information related to the DMF be removed from the 356h form provided in the referencing application? What if there is a conflict between the 3938 and 356h forms?

Answer: Form 3938 does not change the requirement for facility information for the drug substance to be provided to the applicant and included on their 356h form. Any discrepancies between the facilities included in the DMF and those listed in the application are caught during the TCIR process and communicated in an IR to the applicant. Please see the talk by Jayani Perera on the TCIR process for details.

Poster#5: Co-Crystal API: Recommended Documentation

Presenter: Weiqin Jiang

Topic: Recommended Documentation for Co-Crystal

Question: When the reference listed drug (RLD) substance coformer is hydrochloride, can generic drug substance use hydrobromide as coformer; in other words, are hydrobromide or hydrochloride, as coformer, interchangeable?

Answer:

- It depends on if RLD drug substance is HCl salt or a co-crystal.
- If the RLD API is HCl salt then from a regulatory perspective HCl and HBr can't be interchanged in the context of a generic drug per Orange Book definition of Pharmaceutical Equivalence.
- If the pharmaceutical solid qualifies as a co-crystal then it is essentially an API-excipient combination and the coformer can be different in a generic drug.
- Note that both HCl and HBr are strong acids; so both tend to form salts, and are unlikely to form co-crystals.



Presenter: Bapu Gaddam

Topic: Polymeric APIs

Question:

What is the 'Totality of the evidence approach'?

The Totality-of-the-evidence Approach



**Manufacturing
Process**

+

**Orthogonal
Characterization**

+

**Biological
Properties**

Starting material,
Intermediates,
CQAs and CPPs.

Structure confirmation,
Structure signature analysis,
Physicochemical properties,
impurity profile.

Comparative
biological activity
analysis, if
necessary

Literature support/justification for methods used.



Poster #7: Synthetic Peptide APIs of generic complex drug products: Recommendations for API sameness & related impurities.

Presenter: Dr. Ram Randad

Topic: coeluting impurities

Question

- *For the impurities that are common between the DS and RLD, any suggestion for the acceptance criteria if more than one impurity was co-eluted at same retention time?*

Answer

- If the baseline separation of the coeluted peaks could not be achieved indeed, other orthogonal approaches can be followed such as develop a different method or utilize LC/MS extracted ion chromatograms (EIC) to identify and quantitate each individual co-eluting impurity with a different mass in both your DS and the RLD samples.
- If the coeluting impurities are isomeric, an upstream controls in your manufacturing process may be appropriate.
- A detailed report documenting efforts along with justification should be included in your DMF.



Poster #7: Synthetic Peptide APIs of generic complex drug products: Recommendations for API sameness & related impurities.

Presenter: Dr. Ram Randad

Topic: Clarification of impurity limit

Question

- *Could you please clarify if for new impurity the limit to apply is Not more than 0.50% or **not more than 0.5%** as provided under line 243 of the draft guidance?*

Answer

FDA Draft Guidance for Industry: [ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin](#), provides guidance for establishing the active ingredient sameness and related impurity profile studies of your proposed synthetic peptide drug that refer to RLD of rDNA origin. With respect to related impurity limits, the guidance recommends that the Impurity limits, generally, be specified based upon comparative studies between RLD (derived from rDNA) and proposed product and/or safety evaluation (Pharm/tox data and/or immunogenicity). Please be advised that this guidance is not yet finalized and it is still under the comment period and you can submit your comment/s.

Our best thinking at this point is that the new peptide related impurity limit should not be exceeded NMT 0.50%. To support proposed new impurities or higher impurity limit than the RLD, an appropriate justification should be provided.



Poster #7: Synthetic Peptide APIs of generic complex drug products: Recommendations for API sameness & related impurities.

Presenter: Dr. Ram Randad

Topic: Characterization

Question

- Please confirm that for API characterization and Sameness studies 1 API batch is enough. Additionally as far as sameness is concerned please also confirm that one RLD batch can be considered adequate.

Answer

- Yes. For API characterization and sameness studies, Agency recommends that you perform the comparative studies on at least one batch of your proposed API and one batch of RLD.

Poster#8: Regulatory Considerations for Synthetic and Semi-synthetic Oligosaccharide Complex APIs in Generic Products



Presenter: Keduo Qian

Topic: Manufacturing/Fermentation

Question:

- If Starting material of API is manufactured using fermentation, What are the additional requirements to be provided in DMF compared to Starting material of API is manufactured using chemical synthesis?
- If Starting material of API & upstream intermediates of API are manufactured using fermentation, and final intermediate of API is manufactured using chemical synthesis, What are the additional requirements to be provided in DMF compared to Starting material of API and API are manufactured using chemical synthesis?
- If Starting material of API and API itself are manufactured using fermentation, What are the additional requirements to be provided in DMF compared to Starting material and API are manufactured using chemical synthesis?

Answer:



- ICH Q11 and its Q&A document represent Agency's current thinking on the selection of regulatory starting materials for APIs, including semi-synthetic APIs and APIs manufactured by fermentation.
- If the regulatory starting material of an API is manufactured by fermentation, the manufacturing process information, including a brief process description and reagents/solvents used in the starting material process, needs to be provided.
- If an intermediate of the API (semi-synthetic API) or the API itself is manufactured by fermentation, the source material (microorganism) might be appropriate to be considered as the regulatory starting material. In this case, the following information is expected as applicable:
 - Information about the microorganism used for production (i.e. species, type strain) and the description on the origin of the source material (or isolate).
 - A brief description of the procedures used to generate the cell bank system, i.e. master cell bank and working cell bank, and the criteria used for qualification. The information needs include the following as appropriate: process controls in the preparations, storage conditions and retest/expiry date which is supported by the appropriate data, as well as procedures used in testing to determine culture purity and to ensure the absence of contamination.

Poster#8: Regulatory Considerations for Synthetic and Semi-synthetic Oligosaccharide Complex APIs in Generic Products



Presenter: Keduo Qian

Topic: Manufacturing/Fermentation

Question:

- What are the requirements for TSE/BSE compliance for fermented KSM, Fermented API intermediates and Fermented API?

Answer:

- A list of the media components used at each stage of the fermentation process needs to be provided as appropriate. All animal-derived components should be identified and appropriate mitigation steps should be taken to ensure compliances if there is a potential risk of transmitting TSE/BSE.

Poster#9: Quality Considerations for Continuous Manufacturing of APIs



Presenter: Thomas O'Connor

Topic: Batch Size for Continuous Manufacturing

Question: If a manufacturer changes the batch size for an API produced by a continuous manufacturing process what are the recommend actions to approve this type of change.

Answer:

- A range of justified batch sizes can be submitted in an application.
- The recommended action would depend on whether or not the proposed change in batch size is within the firms control strategy.
- If the proposed batch size is beyond the currently defined capability, the supplier should file a supplement.
- The type of supplement (PAS, CBE-30, etc.) would depend on whether or not change in batch size is regarded a major, moderate, or minor change.

Thank You!



- Send questions regarding all posters to:
DMFWorkshop2021@fda.hhs.gov by March 19, 2021 for inclusion in the Q&A sessions during the follow-on webinar on April 9, 2021.