U.S. FOOD & DRUG ADMINISTRATION

Presenter: Vathsala Selvam

Topics: Form 3938, Agent Appointment, Letter of Authorization, Pre-assigned DMF number, Annual Report, and Communications

Form 3938

Question:
Should we submit an Administrative Information Page with every submission when the DMF Form 3938 is submitted?

Answer:

- When the DMF Form 3938 becomes available for use, no need to submit an Administrative Information Page (holder, manufacturer and DMF agent (if appointed) company name, address and contact person information) with every submission since the Form should have the information that an administrative page would have

- If an Agent is appointed for a DMF, please make sure the holder signed Agent Appointment Letter is submitted to the DMF. Just mentioning in the Form is not enough

- If any addition, change or deletion of holder, manufacturer and agent information, providing the updated information in the Form 3938 is not enough, need to submit an amendment to the DMF reporting the change

Agent Appointment

Question:
Is an Agent Appointment Letter mandatory for a secondary DMF?

Answer:

- There is no regulatory requirement to appoint an agent for a DMF

- If the holder decides to appoint an agent to submit and receive communications for either a primary or secondary DMF, then an Agent Appointment Letter should be submitted to each DMF separately

Letter of Authorization (LoA)

Question:
Should the secondary DMF holder include the site details in the Letter of Authorization?

Answer:
In cases where all of the facilities listed in the secondary DMF are not being used to support the primary DMF, we recommend that the specific sites supporting the primary DMF be included in the Letter of Authorization to provide clarity

Letter of Authorization (LoA)

Question:
What is the correct procedure for the withdrawal of a specific LoA in eCTD? Remove the LoA and then add the withdrawal letter or replace the LoA with the withdrawal letter?

Answer:
The best practice would be to submit withdrawal of Letter of Authorization using 'Replace' option in eCTD to withdraw the Letter of Authorization that was already submitted to the DMF

Pre-assigned DMF Number

Question:
How long is a pre-assigned DMF number valid?

Answer:

- A Pre-Assigned DMF number does not expire. If there is any change to the information provided in the request for a pre-assigned DMF number, send an email to dmfquestion@fda.hhs.gov requesting to cancel the assigned number and submit a new request for a new pre-assigned number

- If it has been over three or more years since you received the pre-assigned number, we recommend to send an email to dmfquestion@fda.hhs.gov asking for status. We can verify and let you know if it is okay to use the same pre-assigned number

Annual Report

Question:
Is there a specific amount of time that should be observed in between an amendment and an annual report submission?

Answer:

- No, there is no time duration to be observed in between an amendment and an annual report submission

- Any new change, addition or deletion of information made to the DMF should be reported only by an amendment as they occur

- Quality information should not be included in the Annual Report

Annual Report

Question:
If there is no change to report, is it necessary to send an amendment every year solely to update the long-term stability data or could it be submitted the following year?

Answer:

- There is no requirement to submit stability data annually but if it is updated, it should be submitted to the DMF as an amendment

- An Annual Report needs to be submitted to the DMF every year in order to keep the DMF status active. Please check the webinar on 'Administrative Aspects of Managing a DMF' for information to include in an annual report

Communication

Question:
Would an ANDA holder who references a DMF be notified if there is an issue with the DMF, such as missed Annual Report?

Answer:
Yes, an ANDA holder who references a DMF is notified of any Letter of Authorization issue, User Fee status, Review and Administrative status of a DMF


THANK YOU

U.S. FOOD & DRUG
ADMINISTRATION

PRESENTER: JONATHAN RESNICK

Topics: Managing Electronic DMF Submissions

Presenter: Jonathan Resnick
Topic: Managing Electronic DMF Submission

Question: Should cover letters and forms replace the previous version, or should they always be new?

Answer:

- Cover letters and FDA Forms in headings 1.1 and 1.2 should use an eCTD lifecycle operator of “new” since they describe the contents of the sequence.

- Including a descriptive leaf title (document name) which includes the date of submission can be helpful to the reviewer

Presenter: Jonathan Resnick
Topic: Managing Electronic DMF Submission

Question: Do we need to submit eCTD for a legacy product which has been on the market for long time?

Answer:

- The requirement for submissions to DMFs to be in eCTD is not based on age of the DMF
- All submissions to DMFs, even if the DMF was originally submitted before the requirement went into effect, must be in eCTD
- eCTD requirement applies to Type II, IV and V DMFs
- Submissions to Type III DMFs can be in eCTD or non-eCTD
- Recommend checking the FDA guidance on eCTD submission requirements for additional detail and some scenarios where a waiver may be granted
- Formal title of eCTD guidance is Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

Presenter: Jonathan Resnick
Topic: Managing Electronic DMF Submission

Question: For LOAs that were previously submitted as paper format, can the withdrawals of those LOAs be submitted with cover letter section 1.2 since there is nothing to replace in section 1.4.1?

Answer:

- The draft DMF Guidance (located at https://www.fda.gov/dmf) goes into detail about where to place content regarding a withdrawn LOA in eCTD

***Excerpts from Guidance*:**

"In eCTD section 1.4.3, DMFs must list each party currently authorized to incorporate by reference any information in the DMF (§ 314.420(d)). The list should only contain authorized parties for which LOAs have been submitted and should be updated whenever a new LOA is submitted or an authorized party is withdrawn."

"To withdraw authorization, DMF holders should submit a "Withdrawal of Authorization" letter to the DMF and notify the authorized party. The withdrawal letter should replace the LOA in eCTD section 1.4.1."

U.S. FOOD & DRUG ADMINISTRATION

Presenters: CDR Hanah Pham & LCDR Evelyn Hong

Topic: Drug Master Files from a GDUFA II User Fee Perspective

Presenter: CDR Hanah Pham
Topic: GDUFA II User Fee Requirements

Question: Does a facility manufacturing only API intermediates need to pay a facility fee? And which facility fee does an FDF intermediate manufacturer need to pay when it is identified in an approved ANDA?

Presenter: CDR Hanah Pham
Topic: GDUFA II User Fee Requirements

Answer:

- A facility, that manufacturers only API intermediates, is not subject to GDUFA facility fees.
- However, a facility manufacturing FDF intermediates or in-process FDF mixtures is subject to an FDF facility fee or a CMO facility fee (if eligible) when the facility is identified in an approved generic drug submission.

Presenter: CDR Hanah Pham
Topic: GDUFA II User Fee Requirements

Question: If a new API facility is listed in a pending ANDA, is it required to pay the API facility fee? And, when the ANDA is approved in mid fiscal year, which fiscal year is the facility required to submit the payment?

Presenter: CDR Hanah Pham
Topic: GDUFA II User Fee Requirements

Answer:

- The new API facility is not subject to an annual facility fee until the referencing ANDA becomes approved.
- If the ANDA is approved in the middle of a fiscal year, the new API facility is not required to pay the facility fee for that fiscal year. Instead, the facility will incur the API facility fee for the first time in the next fiscal year.

Presenter: LCDR Evelyn Hong
Topic: GDUFA II User Fee Requirements

Question: If secondary DMF is referred in a primary DMF (i.e., DMF of API-base is referred in a primary DMF of API-Salt, wherein API-base is not being directly used in the finish product manufacturing), is the DMF fee required for the secondary DMF of API-base? Similarly, is the DMF fee applicable for the Type-II DMF intermediate?

Presenter: LCDR Evelyn
Topic: GDUFA II User Fee Requirements

Answer:

- The secondary DMF and API DMF intermediate are not subject to the DMF fee.
- The primary DMF is subject to the DMF fee if referenced in a generic drug submission.

Presenter: LCDR Evelyn Hong
Topic: GDUFA II User Fee Requirements

Question: If the DMF fee is paid for a type-II DMF, does it need to submit another DMF payment for adding a new API facility to replace an existing API facility for that DMF?”

Presenter: LCDR Evelyn
Topic: GDUFA II User Fee Requirements

Answer:

- No. The DMF fee is a one-time fee. Once the fee is paid, no additional payment is required for adding a new API facility.

U.S. FOOD & DRUG ADMINISTRATION

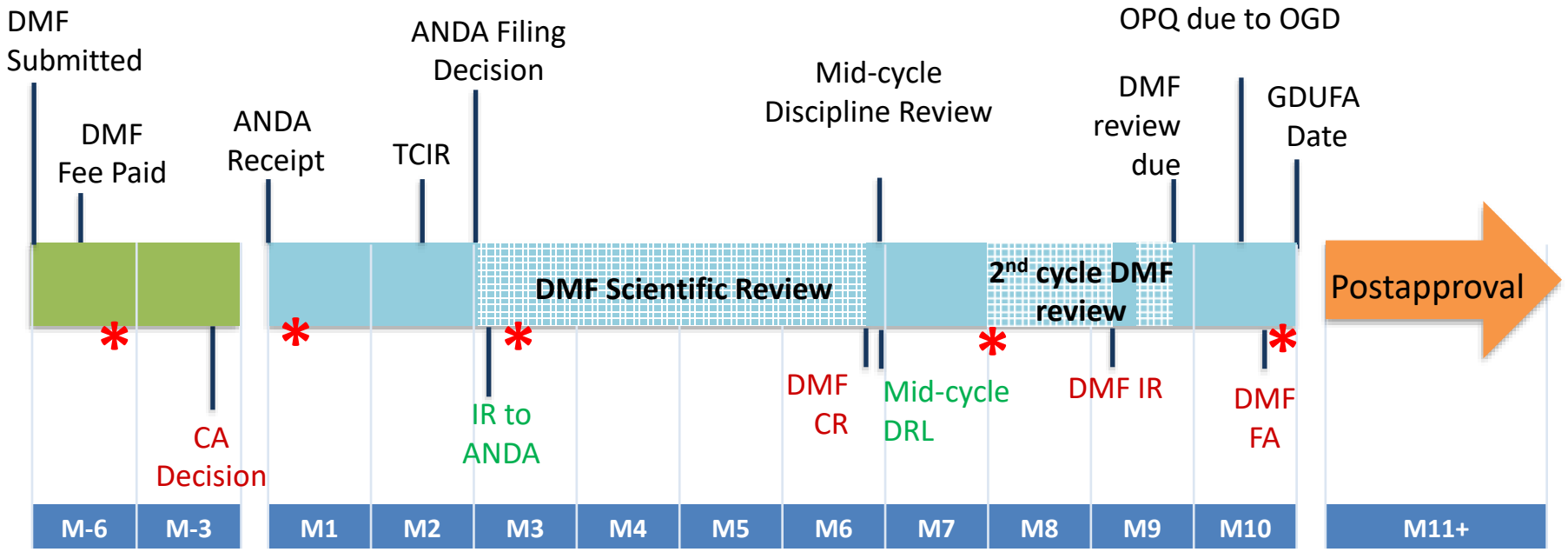
Presenter: Erin Skoda

Topics: Review Timelines, Referencing Applications, Communication

Presenter: Erin Skoda
Topic: Review Timelines, Communication

Question: If the review timeline also depends on the referencing applications, how do I, as a DMF holder, know where we are in the review process?

Answer: We recommend that you stay in constant communication with all of your referencing applicants.



*Suggested communication points between DMF and ANDA

Presenter: Erin Skoda
Topic: Referencing Applications

Question: What is the impact when a DMF is referenced by more than one ANDA? What if the applications are for different dosage forms or indications?

Answer: We consider the DMF as it supports each ANDA. It might be adequate to support one ANDA but inadequate to support another ANDA. Some things to consider when your DMF is referenced by more than one application:

- Drug products has a different maximum daily dose (MDD) as indicated on the label. This may affect ICH Q3A and ICH M7 impurity limits.
- Drug product has a different duration of use. This may affect your ICH M7 impurity calculations.
- Drug product has a different dosage form and/or route of administration. This may require different physical properties or characterization data (e.g., solid state form).

Presenter: Erin Skoda
Topic: Review Timelines

Question: During the ANDA review cycle, can a DMF holder delay the submission of annual report? Will submission of an annual report impact the ANDA review timeline?

Answer: We do not recommend delaying the submission of annual reports. Only quality amendments that are received late in the review cycle may impact the application's timeline. Annual reports should not contain any quality information, and if they do, they will be recategorized as annual report and quality amendment. If you mis-categorize a submission, that may further affect timelines.

Presenter: Erin Skoda
Topic: Communication

Question: Where can we find a list of FDA's common acronyms?

Answer: You may find acronyms defined throughout our recorded presentations. FDA also has a searchable list of acronyms at the link below:

https://www.fda.gov/about-fda/fda-acronyms-abbreviations

U.S. FOOD & DRUG ADMINISTRATION

Presenter: Jayani Perera, PhD

Topics: Completeness Assessment (CA) and Timely Consult and Early Information Request (TCIR)

Presenter: Jayani Perera
Topic: Completeness Assessment (CA)

Question: Can FDA expedite Completeness Assessment review if requested by the holder to reduce the likelihood of a Refuse to Receive (RTR) action on the referencing ANDA?

Answer:

- Yes, FDA will consider requests to expedite the Completeness Assessment from the holder or an authorized party.
- Requests should be sent to DMFOGD@FDA.HHS.GOV and include the following:
  - DMF# and DMF Fee payment date
  - Estimated timeframe for referencing application submission
- Note that industry does very well in submitting DMF fee payments early (three to six months in advance of application submission) such that expedite requests for CA are rarely needed.
- Continued strong performance in this area allows us to consider CA expedite requests when circumstances warrant.
- FDA will internally expedite a CA under the following circumstances:
  - Any error was made on the part of FDA
  - A referencing application is submitted and there is an open CA cycle on the DMF

Presenter: Jayani Perera
Topic: Completeness Assessment (CA)

Question: If an FEI number is not available for a manufacturing, testing, or an advanced intermediate manufacturing facility, does it impact the application filing status or the Completeness Assessment outcome of a Type II DMF?

Answer:

- The *Completeness Assessment for Type II API DMFs under GDUFA Guidance for Industry*, item #16 states, “Central File Number (CFN), Facility Establishment Identifier (FEI), and Data Universal Numbering System (DUNS) numbers should be provided if available.”

- If the FEI number for a manufacturing, additional processing (e.g., micronization), release and stability testing, or critical intermediate facility is missing from the submission, an incomplete comment will be issued.

- This can only impact the filing of an application if it is not resolved prior to the filing decision.

Presenter: Jayani Perera
Topic: Completeness Assessment (CA)

Question: When does the Completeness Assessment review of the DMF start? Is it only after 6 months from the submission date of the DMF?

Answer:

- The Completeness Assessment review starts when the fee status is “Met” and the DMF is “Active” (DMF documentation has been submitted and acknowledgement letter has been issued).

- As stated in the GDUFA II commitment letter, the Agency will strive to complete the initial Completeness Assessment review of 90 percent of Type II API DMFs within 60 days of the later of the date of DMF submission or DMF fee payment. For details please refer to the poster presentation on Completeness Assessments (CAs).

Presenter: Jayani Perera
Topic: TCIR

Question: With new knowledge gained starting material designation that was acceptable in the past may not be acceptable now; you mentioned, and I paraphrase, that TCIR starting material evaluation only applies to DMFs that have never been reviewed. Does this prevent FDA from re-visiting and re-evaluating DMFs that have been reviewed before regarding their starting material designations?

Answer:

- During the TCIR process, starting material evaluation is done only for original DMFs which have never been reviewed.

- Proposed starting material is evaluated using principals outlined in ICH Q11 guidelines.

- For previously adequate DMFs, the starting material will be re-evaluated during full scientific review process *only* if significant changes are made to the manufacturing process or the starting material has been re-designated. Again, the ICH Q11 guidelines will be followed.

Presenter: Jayani Perera
Topic: TCIR

Question: If the DMF holder would like to update the DMF with newly added facilities (e.g. micronized) during the referencing ANDA review cycle, when is the best time for the DMF holder to submit the information to the FDA? Can DMF holder file unsolicited amendment to the DMF? Does it impact approval of the referencing ANDA?

Answer:

There are three scenarios:

- If the newly added facility (manufacturing, testing, or critical intermediate) supports the referencing ANDA, then the DMF holder should notify the Agency in an unsolicited amendment so that the information about the newly added facility can be relayed to the Office of Pharmaceutical Manufacturing Assessment (OPMA). If the newly added facility needs to be evaluated and an inspection is needed, then performance goal date may need to be extended to allow the inspection of the facility before approval.

- If the newly added facility is not supporting the referencing application, then reissue the LOA specifically listing the DMF facilities that do support the application.

- If the newly added facility doesn't support this or other applications now (current application batches are not affected by the new facility), but will be in the future, then the DMF holder should consider adding the facility post approval and delaying submission to the DMF until that time.

U.S. FOOD & DRUG ADMINISTRATION

Presenter: CDR David Skanchy

Topics: GDUFA, DMF issues, and Communication

Presenter: David Skanchy
Topic: GDUFA – API/Excipient mixtures

Question: You mentioned that when an API-excipient mix is for stability purposes, only an API facility fee will need to be paid. Are we talking about "physical" as well as "chemical" stability or only "chemical" stability, which is mentioned in the API definition in GDUFA?

Answer:

- The definition of Active Pharmaceutical Ingredient (API) under GDUFA for the purpose of determining facility fees includes the following:

  "(A) a substance, *or a mixture* when the substance is unstable or cannot be transported on its own……"

- The FDA has interpreted "unstable" to refer to both the chemical and physical stability of the substance. Please refer to the FDA draft Guidance for Industry: *Assessing User Fees Under the Generic Drug User Fee Amendments of 2017.*

- When claiming that the mixture is made for the purpose of mitigating a stability issue and thus qualifying the facility for the GDUFA API facility fee, supporting information such as data and literature references should be provided in the DMF.

Presenter: David Skanchy
Topic: GDUFA –Facility Fees for intermediates

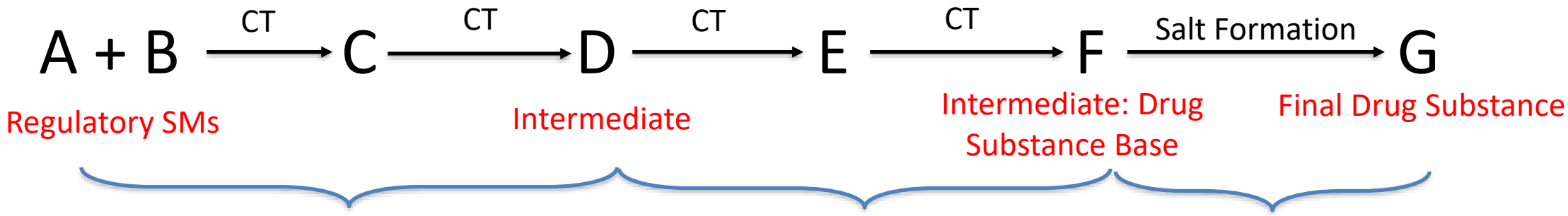
Question: Do facilities manufacturing API intermediates have to pay the GDUFA facility fee or is it just the final API facility that is required to pay?

Answer:

- The nature of the API intermediate determines whether or not the intermediate facility is subject to the API facility fee. In practice, most API intermediate facilities will not incur the fee.
- GDUFA includes the following statement in its definition of API for determining facility fees:

API: "a substance intended for final crystallization, purification, or salt formation, or any combination of those activities, to become a substance or mixture as described in subparagraph (A)."

- Lets apply this definition to the scenario below to see which facilities will incur fees.



Facility 1

No fee incurred.

Intermediate D is one or more CT removed from the API and does not meet the GDUFA API definition.

Facility 2

API Facility Fee Incurred

Intermediate F meets the GDUFA API definition because a salt formation step produces the final API

Facility 3

API Facility Fee Incurred

Final API site

Presenter: David Skanchy
Topic: GDUFA – Drug substance deficiencies in application CR letters

Question: Please explain why sometimes DMF related deficiencies are issued to the ANDA application and not the DMF?

Answer:

- FDA realizes that this situation has been a cause for confusion to industry in some cases.
- It is caused by the following elements of the review process:
  - Different reviewers are responsible for the API related information in the application and the DMF
  - Reviews were largely not synchronized in time
  - Lack of coordination and communication between the DMF and application reviewers
- FDA is addressing these issues through the implementation of the Integrated Quality Assessment (IQA) – Aligned Teams (AT) review process (August 2020) to reduce inconsistencies in the content and timing in application and DMF letters
  - Reviewers from different disciplines work together on multiple projects
  - Improved synchronization of reviews by members of the team
  - Improved communication between members of the team
- Please refer to Poster#10 on ANDA Aligned Teams by Steve Kinsley and Wei Song for details on the IQA-AT review process

Presenter: David Skanchy
Topic: GDUFA – Available for Reference requirements for DMFs in supplements

Question: Could you please clarify whether the DMF must be listed in the DMF Available for Reference list when we are filing a PAS for new strength addition to the approved ANDA using the same DMF (i.e. no change in API source)?

Answer:

- If the Drug Master File was appropriately referenced by an LoA prior to the start of GDUFA on October 1, 2012 then there is no requirement that the DMF pay the fee or be on the Available for Reference list to support the Prior Approval Supplement for that application.

- If the DMF were being referenced for the first time by that application in the recently submitted PAS then the Available for Reference requirements would apply.

- Note that when the DMF referenced in a PAS must meet “Available for Reference” requirements that the FDA can do the following:
  - Refuse to Receive the supplement when subject to a filing review (e.g. new strength supplement)
  - Suspend review activity until requirements are met when the supplement is not subject to a filing review (e.g. alternate API source).

Presenter: David Skanchy
Topic: Communication – Unsolicited Amendments to DMFs

Question: Often the ANDA under review is not the only customer referencing a DMF. It is difficult for the DMF holders to provide adequate and timely continued support to all customers if they are concerned about an extended timeline due to what may be a very simple 'unsolicited' submission. How can Industry effectively deal with these situations especially for older DMFs that are multiply referenced by approved products?

Answer:

- FDA does understand that these situations can and do arise and we have the following recommendations:
  - Make sure you are aware of the action dates for open referencing applications by getting that information from your customers
  - Let your customers know you are planning an unsolicited amendment to the DMF and your proposed timing so they are aware
  - Reach out to us at DMFOGD@FDA.HHS.GOV to seek further advice (noting that we cannot discuss application goal dates with you)
  - Understand the consequences (i.e. goal date extensions) when an unsolicited amendment must be submitted
  - Note that in our experience most (but not all) unsolicited amendments can come in with timing that does not adversely impact an application timeline
  - In some cases the DMF holder must make a business decision that won't be completely satisfactory to all customers

Presenter: David Skanchy
Topic: Communication – Unsolicited Amendments to DMFs

Question: Are Annual Reports and Letters of Authorization (LoAs) considered unsolicited amendments that could adversely impact an application timeline and delay an approval?

Answer:

- Annual Reports and Letters of Authorization are administrative amendments and are not treated as unsolicited amendments in the same way as amendments with contain quality information
- Administrative amendments do not trigger a review and cannot result in goal date extensions or deferrals nor can they impact the adequate/inadequate status of the DMF
- Other types of common administrative amendments are Change in Holder, Change in Subject, New US Agent Appointment letter
- The only administrative amendments that can impact an application are an LoA withdrawal or a DMF closure request
- Note that Annual Reports should not contain any quality information, including updated stability data. If they do they will be treated as both an Annual Report and a Quality Amendment.

U.S. FOOD & DRUG ADMINISTRATION

Presenter: Brian Connell

Topic: Postapproval Changes to Drug Substances Draft Guidance

Presenter: Brian Connell
Topic: Postapproval Changes to Drug Substances

Questions:

A change in the manufacturing process of a drug substance results in the appearance of new process impurity X in an intermediate and therefore there is a new non-equivalent impurity profile when compared to the pre-change intermediate. A drug substance manufacturer adds a test to control this process impurity X at its point of origin and demonstrates that Impurity X and its potential downstream analogs are properly controlled based on data generated for a risk assessment considering ICH Q3A, Q3C, Q3D, and M7 guidelines. Even though impurity profile is not exactly the same before and after the change, is this approach acceptable?

If yes, how much method validation data should be submitted?

Presenter: Brian Connell
Topic: Postapproval Changes to Drug Substances

Answer (page 1 of 2):

Pre-and post change impurity profiles are not required to be equivalent, so yes, this approach is acceptable.

Because of the manufacturing change, the acceptance criteria for the new Impurity X in the intermediate specification should be justified based on a risk assessment that includes a Hazard Classification per Section 6 of ICH M7.

ICH M7 Section 8.1 discusses possible control strategies for process impurities. The updated control strategy should address downstream impurity analogs, if necessary. The Agency considers this necessary when the new Impurity X is controlled in the intermediate at a level higher than the appropriate drug substance limit for Impurity X and its potential downstream analogs, based on either ICH Q3A or M7, as applicable.

Support for a control strategy could include results of a spike/purge study, a calculated purge factor analysis, a demonstration of downstream detection and quantitation of the relevant impurities by the routinely used impurities methods, or some combination of all of these approaches.

Answer (page 2 of 2):

Analytical methods should be developed with sufficient specificity and sensitivity for their intended use. Unless the routine drug substance methods are being updated, full method validation does not need to be submitted. However, we generally recommend that some basic method information is provided, including a basic method description and a statement of the limits of detection and quantitation.

Presenter: Brian Connell
Topic: Postapproval Changes to Drug Substances

Question: Our product was approved prior to the adoption of the ICH M7 mutagenic impurities guidance and a risk assessment for potentially mutagenic impurities was not performed at the time of approval. We are transferring the drug substance manufacturing process to a new supplier, but no changes have been made to manufacturing process, reagents, or specifications. Do we need to conduct a risk assessment now?

Presenter: Brian Connell
Topic: Postapproval Changes to Drug Substances

Answer:

Generally, no, a new risk assessment is not necessary if the supplier change is the only change. ICH M7 Section 4.1: "Changing the site of manufacture of drug substance, intermediates, or starting materials or changing raw materials supplier will not require a reassessment of mutagenic impurity risk."

However, a risk assessment may be necessary if the change falls into the scope of ICH M7 (Section 2). Specifically, if there is a change made in indication or dosing regimen which significantly affects the acceptable cancer risk level, ICH M7 will apply.

For example, if the new supplier is added due to market demand for a new referencing product with the same drug substance but with a higher maximum daily dose (MDD) than the originally approved product, a risk assessment would be necessary.

Note that a risk assessment would be necessary in this example even if a new supplier was not added, due to the increase in the MDD of a referencing product.

Presenter: Brian Connell
Topic: Postapproval Changes to Drug Substances

Question: Do the requirements and recommendations in the Postapproval Changes to Drug Substances Draft Guidance apply to drug substances used in combination products?

Presenter: Brian Connell
Topic: Postapproval Changes to Drug Substances

Answer:

Yes, the recommendations in the guidance apply to multi-API drug products and each drug substance therein. For example, if the drug product is an oral tablet containing both APIs A and B, the guidance applies to each API, A and B, separately, and the combination final drug product containing APIs A and B.

Presenter: Brian Connell
Topic: Postapproval Changes to Drug Substances

Question: If a change is made and there is a new impurity in an intermediate, and the impurity, as well as the possible downstream analogs formed from this impurity, are shown to be absent in three batches of drug substance, would this be sufficient to avoid updating the specifications of the intermediates and the drug substance?

Answer:

A central principle of the Draft Guidance is that the manufacturing process can be adequately assessed by comparing three consecutive batches of pre- and post-modification material.

If the required ICH M7 and Q3D risk assessments have been completed and the new impurity and its potential analogs are absent from the drug substance based on application of the appropriate threshold limits, then yes, the drug substance impurity profiles, pre- and post-change, would be considered to be equivalent and no specification change to the intermediates or the drug substance would be required.

U.S. FOOD & DRUG ADMINISTRATION

Presenter: Cassandra Abellard

Topics: Hidden Facilities, Critical Intermediates

Presenter: Cassandra Abellard
Topic: Hidden Facilities and Critical Intermediates

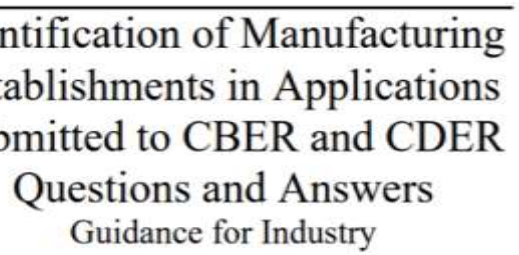
Question:

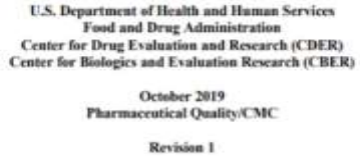
Does the information for the QA contact at the site need to be provided in the DS section or does that information belong on the form 356h?

Answer:

The information for the QA contact at the site should be provided in the DS section as well as on the 356h *if* the QA contact is the contact person for the site.

FDA Guidance for Industry "*Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers*" has the following example table for this information (this should follow a table of facility information):


Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers
Guidance for Industry


U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics and Evaluation Research (CBER)

October 2019
Pharmaceutical Quality/CMC

Revision 1

Corresponding names and titles of each facility's onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Presenter: Cassandra Abellard
Topic: Hidden Facilities and Critical Intermediates

Question:

Do the following facilities need to be included in S.2.1 and/or on the Form 356h?

1. Pilot scale API production sites?
2. One-time testing sites?
3. DS stability storage site?
4. DS storage site?
5. Raw material testing sites?
6. Critical intermediate sites?

Answer:

The 356h should include all drug substance and drug product manufacturing and testing sites as well as critical intermediate manufacturing and testing sites. In general, any site supporting commercial manufacturing of your product should be listed on the form 356h

Per The FDA Guidance for Industry "*Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers*":

- Module 3 should contain all facilities listed on Form FDA 356h, as well as R&D manufacturing and testing sites that generated data in support of the application. This would include one-time testing sites.
- Module 3 should also contain testing labs that perform functions integral to the control strategy. This includes any testing sites that generate release data, stability testing to support the application, as well as analytical development sites.
- All manufacturing and control sites should be in either the drug substance (3.2.S.2.1) or drug product (3.2.P.3.1) sections of Module 3. If you are not sure if the site should be included, add it to Module 3.

Presenter: Cassandra Abellard
Topic: Hidden Facilities and Critical Intermediates

Question:

Can you give an example of what should be listed for responsibilities of each facility in S. 2. 1 for firms that perform multiple operations? Single test?

Answer:

The FDA Guidance for Industry "*Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers*" recommends the following:

- Clearly identify all facilities associated with your application in a table format at the beginning of the relevant section in Module 3.
- Include this summary table at the beginning of each relevant section in Module 2.
- Include the full establishment name and establishment address where the manufacturing function is performed.
- Include the FEI number and specific manufacturing operations and responsibilities for each facility, including type of testing and drug master file (DMF) number, if applicable. Provide the name and title of an onsite contact person, including their phone number, fax number, and email address.
- For testing sites in particular, please state specific test(s) being performed
- If you decide to use a table format, the following is recommended:

Facility information:

Site Name	Site Address	FDA Establishment Identifier (FEI)	Drug Master File Number (if applicable)	Specific Manufacturing Responsibilities or Type of Testing [Establishment Function]
1.				
2.				

Presenter: Cassandra Abellard
Topic: Hidden Facilities and Critical Intermediates

Question:

Do hidden facilities apply to NDA DMFs also?

Answer:

Yes, hidden facilities apply to NDA DMFs

FDA U.S. FOOD & DRUG ADMINISTRATION

Presenter: Wei Liu

Topics: Hidden Facilities and Critical Intermediates

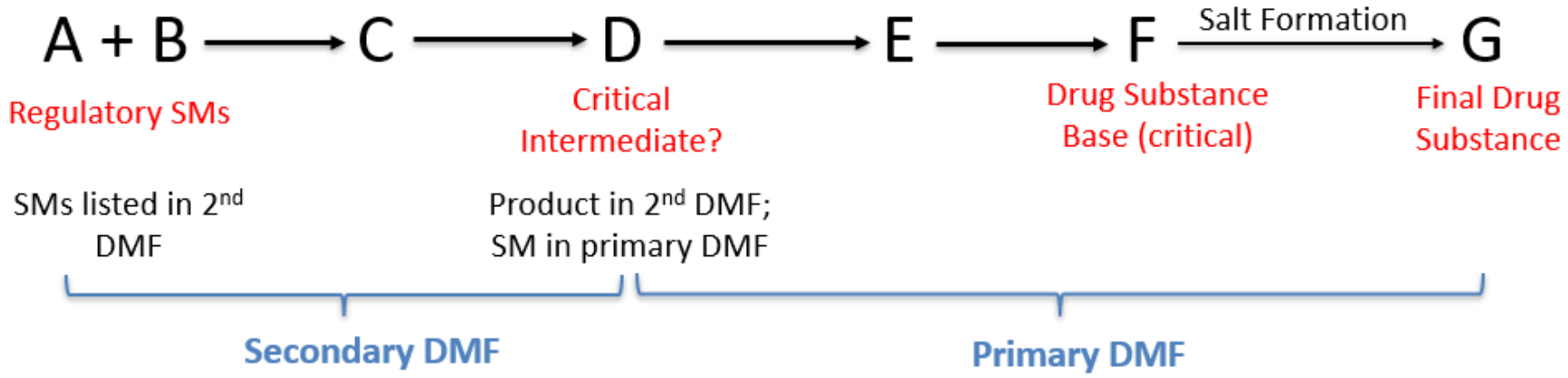
Presenter: Wei Liu

Topic: Critical Intermediates and Facilities

Question: Should DMF holder update the 3.2.S.2.1 section to include the sites of the secondary DMF?

Answer: On slide 16 of the presentation:

"The determination of critical intermediate is based on complete manufacturing process from the regulatory SM to final API. The regulatory SM may NOT be the "SM" listed in S.2.3 in your DMF when a secondary DMF is referenced."



- If a secondary DMF is referenced, list the DMF number and manufacturing site information as appropriate in section 2.1 in the primary DMF.
- Provide the LOA for the secondary DMF in section 2.1/2.3 in the primary DMF.
- Clearly indicate which intermediate is manufactured at the intermediate site.
- Communicate to ANDA applicants so that the facility information can be included in the referencing ANDA applications.

U.S. FOOD & DRUG ADMINISTRATION

Presenter: Jay Jariwala

Topic: API Facility Inspection

Presenter: Jay Jariwala
Topic: API Facility Inspection

Question: Can I remove an API site from my application if it is OAI and substitute it with another site? If so, what should I consider?

Answer

- Yes, you can.
- Communicate and follow guidance provided by the responsible office handling your application
- We recommend you evaluate how CGMP deviations may have affected the various data you have provided in support of the application
- Also, other site will still be evaluated whether it will require a pre-approval inspection

Presenter: Jay Jariwala
Topic: API Facility Inspection

Question: What can trigger API inspection?

Answer

- FDA may inspect a drug manufacturing facility:
  - For surveillance to ensure the quality of drugs intended for the U.S. market (Routine surveillance inspections)
  - To evaluate its readiness in support of an application (Pre-approval inspections)
  - When FDA has information concerning the quality of drugs manufactured and supplied by the firm (For-cause inspections)

Presenter: Jay Jariwala
Topic: API Facility Inspection

Question: If API is manufactured by a contract manufacturer, does the contract manufacturer need to validate the API process?

Answer

- Regardless of who manufactures your product or the agreements in place, you are required to ensure that these products meet predefined specifications prior to distribution and are manufactured in accordance with the FD&C Act

Responsibilities

Owners

- Final approval or rejection of API for use and distribution
- Cannot be delegated to Contracted Facility or via a Quality Agreement

Contract facilities

- CGMP for all operations performed, including promptly evaluating and addressing manufacturing or quality problems
- Quality Unit product disposition (e.g., release, reject) decision for each operation it performs

Everyone

- Compliance with all CGMP
- Product quality
- Patient safety

Presenter: Jay Jariwala
Topic: API Facility Inspection

Question: Is it expected that an API manufacturer will be inspected every 3 years?

Answer

- There is no set frequency
- FDASIA changed the requirement for the FDA to inspect domestic and foreign drug manufacturing sites “in accordance with a ***risk-based*** schedule”
- See slide 5 of the webinar presentation for the factors FDA considers in evaluating whether to inspect a facility

Presenter: Jay Jariwala
Topic: API Facility Inspection

Question: If my facility is on import alert, can I ship API to a manufacturer outside the US to make drugs intended for the US?

Answer

- No
- A facility on import alert can not supply drugs to the US market, directly or indirectly

U.S. FOOD & DRUG ADMINISTRATION

Presenter: Bapu R Gaddam

Topic: Regulatory Considerations in Demonstrating Complex API Sameness

Presenter: Bapu R Gaddam
Topic: Regulatory Considerations in Demonstrating Complex API Sameness

Question: What is the definition of “complex API”?

Answer:
GDUFA Commitment letter: Complex Product generally includes: Products with complex active ingredients (e.g., peptides, polymeric compounds, complex mixtures of APIs, naturally sourced ingredients); complex formulations (e.g., liposomes, colloids); complex routes of delivery (e.g., locally acting drugs) or complex dosage forms (e.g., extended release injectables). The composition, quality and in vivo performance of these complex drug products are highly dependent on manufacturing processes of both the active ingredient as well as the formulation. All active substance structures that cannot be fully characterized and/or described by conventional physicochemical analytical methods. The current thinking is any active substance structures that needs orthogonal characterization methods with product specific analytical techniques and/or also the characterization is dependent on the manufacturing process and functional data are considered as complex API.

Question: Are botanical drugs complex APIs?

Answer: As described in the draft guidance for 'Botanical drugs the characterization of drug substance used in the botanical drugs', product specific techniques and methods for the manufacturing and characterization of drug substances are used in botanical drugs.

However, the complexity is dependent on the individual drug substance and/or drug product. The guidances and recommendations are applied based on the properties of the individual drug substance and drug product.

Presenter: Bapu R Gaddam
Topic: Regulatory Considerations in Demonstrating Complex API Sameness

Questions: Following are related to guidance on peptide: "*ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin Guidance for Industry*".

a: In the case of a peptide with an official USP monograph that is manufactured by recombinant technique and the same peptide submitted by DMF holder is manufactured using a synthetic process, what is FDA's stance on API sameness? Are there any additional requirements/techniques that should be used to demonstrate API sameness?
b: For Linaclotide, being a synthetic peptide, do we need to follow the draft guidance (synthetic vs recombinant) for control of impurities?

Presenter: Bapu R Gaddam

Topic: Regulatory Considerations in Demonstrating Complex API Sameness

Answer: If the peptide is official in USP and manufactured by recombinant technique and same peptide submitted by DMF holder and it is manufactured using synthetic process, then the DMF holder is advised to follow our recommendations mentioned in our Draft guidance for industry: "*ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin Guidance for Industry*". As per this guidance, submission of an ANDA for a proposed generic synthetic peptide for which the reference listed drug (RLD) is a peptide of rDNA origin, generally, would be appropriate if the applicant show the API sameness as described in this draft guidance. Whether an application should be submitted as an ANDA or as an application submitted pursuant to section 505(b)(2) of the FD&C Act, may depend on the proposed product's impurity profile.

As per our current thinking, we advise you to follow our recommendations mentioned in this Draft guidance for industry for the control of related impurities in Linaclotide.

Specifically, the above said guidance covers the following five peptide drug products: glucagon, liraglutide, nesiritide, teriparatide, and teduglutide.

Presenter: Bapu R Gaddam
Topic: Regulatory Considerations in Demonstrating Complex API Sameness

Question: Regarding API sameness:

a. Do the API sameness requirements described in your presentation also apply when qualifying an alternate API supplier for an IR tablet?
b. Does an ANDA applicant need to repeat sameness/comparative studies of drug product with RLD if the stability data of the batches made with new API is trending similar to batches with approved API? Is similarity in the stability data of batches made with new API with approved API sufficient to demonstrate that there is no negative impact on product quality, safety, potency, and purity?

Answer:

An ANDA generally must contain information to show that the proposed generic product (1) is the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) and (2) is bioequivalent to the RLD. The API sameness should be established for the API obtained from the additional new source or alternate API supplier. The data required depending on the nature of the drug product and drug substance.

The stability data is useful to establish the expiry date of the drug product. Stability data of drug product does not establish the sameness of API from the new source.

U.S. FOOD & DRUG ADMINISTRATION

Presenter: LT Suresh Jayasekara

Topics: GDUFA, DMF issues, and Communication

Presenter: Suresh Jayasekara
Topic: GDUFA – Complex APIs

Question: For peptide drug substances, is it necessary to perform the bio-assay test for characterization purposes? Is a routine bio-assay release test complementary to the assay by HPLC required in the drug substance specification?

Answer:

- Bio-assay test is useful only at the formulated peptide API (Drug product) stage. Therefore, in the complex peptide DMF submission, the bio-assay test is neither required in the drug substance characterization section nor in the DS release specification.

Presenter: Suresh Jayasekara
Topic: GDUFA – Complex APIs

Question: Another topic that we would like to clarify is peptide sequencing as a proof of primary structure. Is it expected to be demonstrated once in the context of RLD sameness and characterization, or should it be part of the drug substance specification routine identification test?

Answer:

- Peptide sequence analysis is one of the key characterization methods that you have to provide along with other primary structure characterization methods in the section 3.2.S.3.1 of the DMF. It is not required to add the peptide sequence analysis test as a part of routine identification test in the drug substance specification.

Presenter: Suresh Jayasekara
Topic: GDUFA – Complex APIs

Question: Does the agency expect to obtain generic drug characterization in context of aggregation/oligomerization state at API stage in the DMF? If yes, should it be a part of RLD sameness study?

Answer:

- The evaluation of higher order structures, polymer/oligomer aggregation states are meaningful only at the formulated API (Drug product) stage; therefore, higher order structures, polymer/oligomer aggregation studies are not required for drug substance stage (e.g., in the DMF).

Presenter: Keduo Qian

Topic: Complex API

Question 1:

- For Complex APIs, when the dose is very low, how to extract the API from RLD finished dosage form to establish sameness? For example, when the RLD is a metal complex, can FDA provide the extraction procedure or is FDA aware of how to extract the molecule from a complex?

Question 2:

- What kind of information can we obtain from a Pre-ANDA meeting?

Answer:

- The sample preparation and comparison strategy is different case by case. FDA doesn't have a specific recommendation on how to extract the complex API from the RLD finished dosage form in order to establish drug substance sameness. However, the general principle was laid out in poster #8 and it is up to the applicant to demonstrate a "complete and clean recovery (per label claim) of the drug substance from RLD, so that the analytical results are representative".
- In certain circumstances, for example when the finished dosage form is a relatively simple injection or the drug substance constitutes the absolute majority of the drug product, a direct head-to-head comparison with the RLD may be acceptable.
- In other circumstances, the ANDA applicant is welcome to submit a pre-ANDA meeting package to discuss specific scientific issues or questions (e.g., a proposed study design, study expectations, etc). The FDA expects the prospective applicant has enough knowledge of the complex product to allow FDA to provide appropriate feedback that will advance product development early in the process (i.e., the applicant should have generated its own data to be discussed).

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

Presenter: Keduo Qian

Topic: Manufacturing/Fermentation

Question 3:

- After approval of ANDA, if the ANDA applicant wants to use an alternate API, does all the characterization done at the time of original submission for API need to be repeated for the alternate API? Or is it enough that the referencing DMF of alternate API submits the DS sameness characterization?

Answer:

- The request for repeated sameness characterization tests will be evaluated on a case-by-case basis. The DMF of the alternate API should establish the complex API sameness. Depending on the finished dosage form preparation process and its impact on the drug substance structure features, some sameness tests may need to be repeated. The ANDA applicant is welcome to consult with the FDA on specific questions.