# Poster#10: Optimization of Integrated Quality Assessment (IQA)

Presenter:  Steven Kinsley
Topic: Balanced Workloads

Question: How does FDA maintain  a balanced workload among these Aligned Teams for ANDAs and DMFs?

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**Answer:**

- The major issues involved in balancing workload is a determination of the capacity for the individual team and an assessment of the relative challenges presented in each submission.

- For ANDA submissions, the first triage is to determine whether the dosage form is a liquid or solid.

- Next the ANDA is triaged to determine expertise required and challenges in the review.

- Reviews are then assigned to balance work between teams.

- Team Leaders then balance work between assessors.

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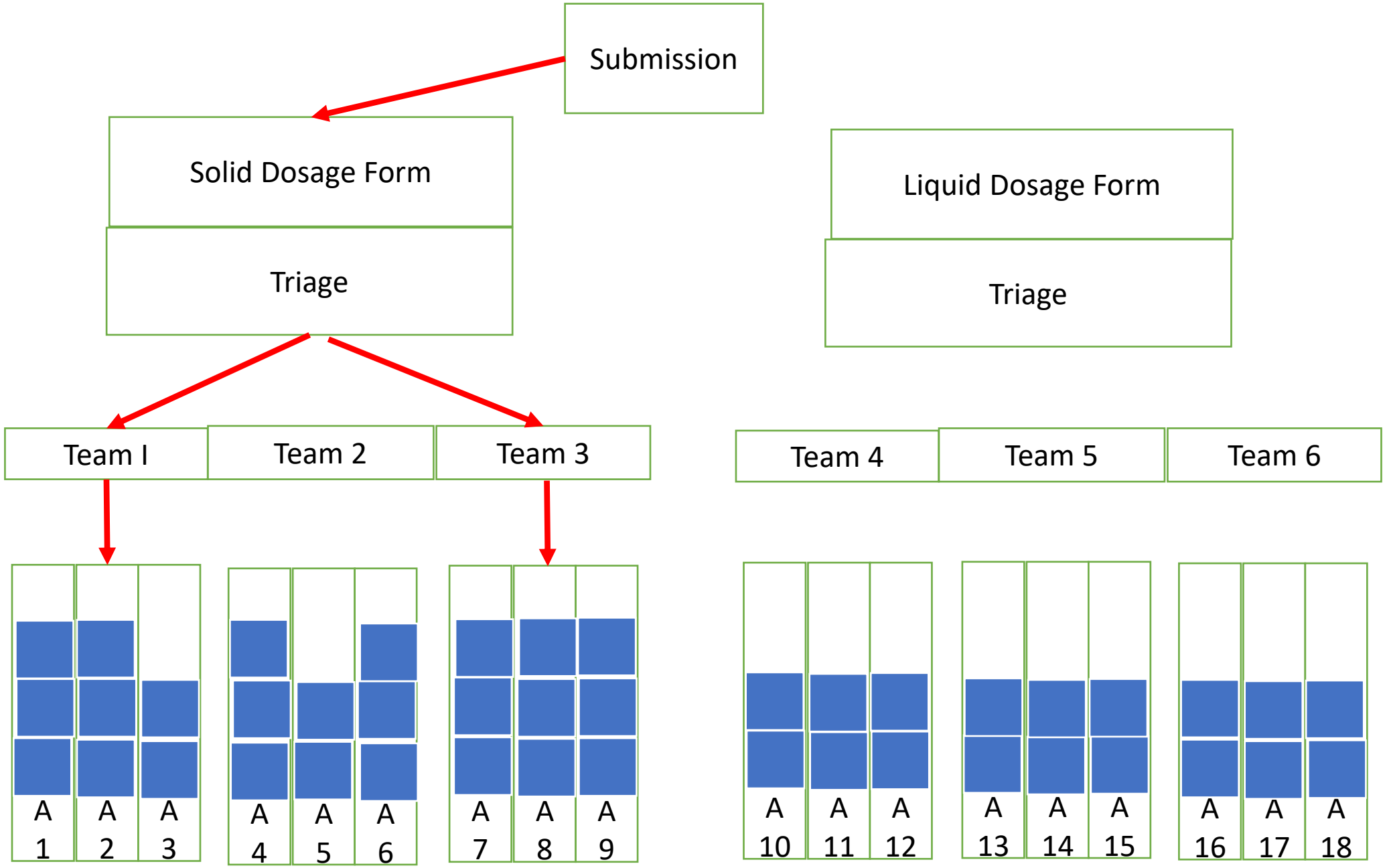


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# Poster #11: Review of Secondary Type II Drug Master Files

Presenters:  Madhusudhan Gowravaram and CDR David Skanchy

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# Poster #11: Review of Secondary Type II Drug Master Files

Presenters: Madhusudhan Gowravaram and CDR David Skanchy

Question:
The slide #12 in the presentation indicates that it is acceptable to reference another API DMF as a secondary DMF for a critical intermediate as long as it is clearly mentioned in the primary DMF that the reference is only for a particular intermediate. One clarification that may be very helpful regarding referencing a secondary DMF partially, is regarding how the primary DMF will be deemed adequate and eventually how the ANDA's approval status will be determined, if the secondary DMF is deficient, albeit for deficiencies that are not related to the particular critical intermediate (ex, API not characterized properly, specification and analytical methods of API deficient, failures in API stability, API testing facilities are not in compliance) it is referencing.

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# Poster #11: Review of Secondary Type II Drug Master Files

Presenters:  Madhusudhan Gowravaram and CDR David Skanchy

Answer:

- As a general principle all DMFs are reviewed in the context of how they are referenced.  So if a DMF has a partial reference by another DMF for an intermediate material the primary DMF and the application it supports are only impacted by the regulatory status (adequate or inadequate) of that specific referenced information.

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Answer:

- As a general principle all DMFs are reviewed in the context of how they are referenced.  So if a DMF has a partial reference by another DMF for an intermediate material the primary DMF and the application it supports are only impacted by the regulatory status (adequate or inadequate) of that specific referenced information.
- The secondary DMF could be adequate for the intermediate information presented in it even if at the same time it was inadequate for the final API due to the reasons not related to the quality of the intermediate.

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Answer:

- As a general principle all DMFs are reviewed in the context of how they are referenced. So if a DMF has a partial reference by another DMF for an intermediate material the primary DMF and the application it supports are only impacted by the regulatory status (adequate or inadequate) of that specific referenced information.
- The secondary DMF could be adequate for the intermediate information presented in it even if at the same time it was inadequate for the final API due to the reasons not related to the quality of the intermediate.
- In terms of facilities, only the secondary DMF facilities associated with the manufacture of the intermediate (assuming it is a critical intermediate) would be listed in the A/NDA application and impact the approvability of the A/NDA.

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# Poster #11: Review of Secondary Type II Drug Master Files

Presenters:  Madhusudhan Gowravaram and CDR David Skanchy

Question:
Is Secondary DMF (Key starting material / Intermediate) manufacturing site inspection mandatory for review of respective drug substance DMF and approval of ANDA?

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Question:
Is Secondary DMF (Key starting material / Intermediate) manufacturing site inspection mandatory for review of respective drug substance DMF and approval of ANDA?

Answer:
The manufacturing process of all intermediates including those described in a secondary DMF are subject to GMP per ICH Q7. We recommend that all critical intermediate sites be listed in the referencing application's 356h form.  Determination on whether an intermediate facility needs a comprehensive evaluation or inspection is made on a case-by-case basis using risk assessment principles as outlined in ICH Q11 as well as using the manufacturing process information and control strategy presented in both primary and secondary DMFs.

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# Poster #11: Review of Secondary Type II Drug Master Files

Presenters:  Madhusudhan Gowravaram and CDR David Skanchy

Question:
What is the validity period for a LOA? If DMF holder issues LOA at the time of filing ANDA is it not valid till the approval time?

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Presenters:  Madhusudhan Gowravaram and CDR David Skanchy

Question:
What is the validity period for a LOA, if DMF holder issues LOA at the time of filing ANDA is it not valid till the approval time.

Answer:
There is no expiry on an LoA and it is valid until an updated LoA is issued by the holder or until the holder withdraws it.

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# Poster#12: USP Pending Monograph Process and USP Compliance for Industry

Presenter: Yan Ma

Topic: USP Pending Monograph Process

**Question:** In case, based on method equivalency reports if in-house methods found superior to the USP methods, after FDA approval, can applicant initiate USP-PMP process to have in-house methods added to the USP-NF monographs?

**Answer:** We recommend that the applicant initiates the USP-PMP process concurrently with the submission of the application to FDA to avoid delay in the approval of the application. The applicant may petition to add their in-house methods to the USP-NF monographs after FDA's approval. However, this approach is not the USP-PMP process. It is the currently established process for the revision of an official USP monograph.

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# Poster#12: USP Pending Monograph Process and USP Compliance for Industry

Presenter: Jenny Wang

Topic: USP Compliance for Industry

**Questions:** When USP monograph method is adopted for testing of a drug substance, should complete method validation be performed (or) method verification with system suitability, Specificity, precision, Quantitation limit and solution stability is sufficient?

Is this applicable to adopt USP monographs for post approval changes and also for approved ANDAs?

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# Answers:

- According to 21 CFR 211.194(a)(2), users of analytical methods described in USP–NF are not required to validate the accuracy and reliability of these methods, but merely verify their suitability under actual conditions of use. Therefore, if a USP monograph method is adopted for testing a drug substance, a complete method validation as per USP <1225> is not required, while a method verification as per USP <1226> including system suitability, specificity, precision, quantitation limit (not applicable to assay methods) and solution stability should be sufficient.

- The above response is also applicable when the USP monograph methods are adopted for post approval changes to drug substances. We are not assessors for ANDA applications and we are not in a position to address any questions related to ANDAs.

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# Poster#13: Evaluation of Elemental Impurities in Drug Substances

Presenter: Donglei Yu

Topic: Elemental Impurities

**Question**:

In the presentation, it is said that "FDA requires DMF holders to provide risk assessment of elemental impurities for the manufacturing process of drug substances." Where is this written in a guidance? It would be really helpful it you could point us to the right direction for this requirement.

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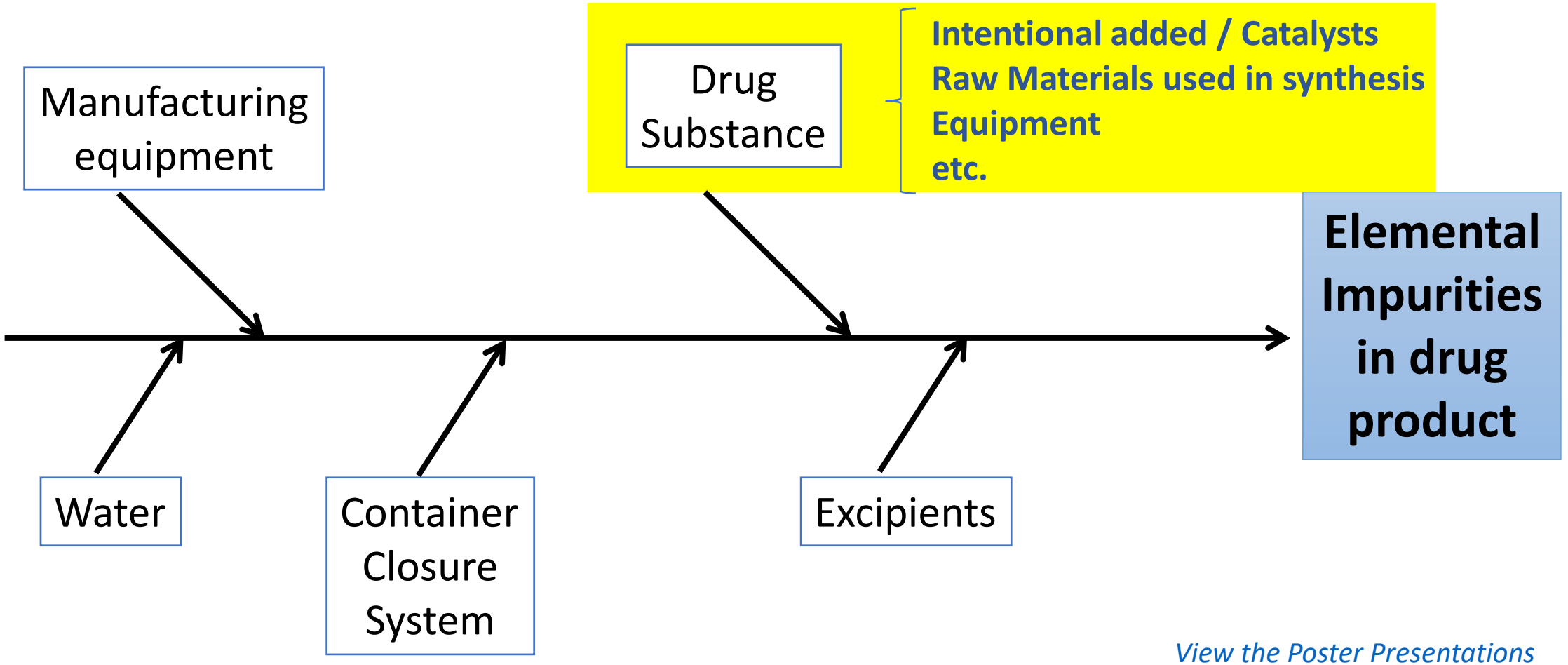
# Answer:

- ICH Q3D has recommendations on applying a risk-based approach to control elemental impurities and permitted daily exposure (PDE) for new finished drug products and new drug products containing existing drug substances.

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# Answer - Con’t:

- Information for this risk assessment includes but is not limited to: data generated by the applicant, **information supplied by drug substance** and/or excipient manufacturers, and/or data available in published literature.

- Usually, the drug product applicants do not have the information on drug substance manufacturing process. Although ICH Q3D applies to finished drug products, the DMF holders are highly recommended to perform risk assessment of elemental impurities in their drug substance and work closely with each drug product applicant to ensure compliance.

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**Question**:

On Slide 12, you said ‘Elemental impurities to be treated like related substances and to be tested routinely’, do you mean catalysts used or all elemental impurities?

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# Example 2, Elemental impurities not Covered by ICH Q3D

***Drug Product***: Lanthanum Carbonate Chewable tablet

***Drug Substance***: Lanthanum Carbonate

***Maximum Daily Dose***: 3g/day as element lanthanum, ~6g/day of Lanthanum Carbonate Pentahydrate

*Elemental impurities should be treated like "related substances" and routinely controlled in drug substance specification.*

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**Answer – Con't**:

- For most DMFs, the elemental impurities to be evaluated can be found in Table 5.1 of ICH Q3D. Please refer to Slides 5-9 for element classification, PDEs per route of administration, limit calculation, and data to be included in the submission.

- ICH Q3D has included most catalysts used by the pharmaceutical industry. If a drug substance uses a catalyst which is not listed in Table 5.1, this element needs to be evaluated since it is intentionally added. Please refer to Slide 11 for the determination of the PDE.

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# Poster#14: • Mutagenic Impurities from a Drug Substance Perspective: Highlights from the ICH M7 Question and Answer Draft Document

Presenter: David Green
Topic: Mutagenic Impurities in old APIs (Drug substances) that have existing monographs

Question:
For existing old APIs that have a USP & Ph.Eur Monograph, is an evaluation/ risk analysis required for Mutagenic Impurities from a Drug Substance at the time of DMF submission?

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Answer:
In order to classify impurities per the DMF holder's unique manufacturing process, all new Drug Master Files submitted to the Agency should perform an impurity hazard assessment per ICH M7 (Please refer to Section 6 of the ICH M7 Guidance) regardless of whether the API has an existing USP & Ph.Eur Monograph. This should be done at the time of filing.

The exceptions are those APIs that our out of the scope of M7 (Please refer to Section 2 of the Guidance and ICH M7 Q&A (Step 2) #s 2.1, 4.1, 6.3):

- Biological/biotechnological, peptides, oligonucleotides, radiopharmaceutical, fermentation, herbal, crude products of animal or plant origin.
- Drugs intended to be used for advanced cancer.
- API's that are genotoxic at therapeutic concentrations.

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# Poster#15: Establishing Impurity Acceptance Criteria As Part of Specifications for DMFs Based on Clinical Relevance

Presenter: Dr. Yongjun Gao

Topic: Drug product dose

**Question**: If the drug substance DMF holder does not know the drug product dose, how can a limit be set based on clinical relevance?

**Answer:** It is imperative that the drug substance DMF holder communicates with the drug product applicant regarding the intended use of the drug substance and the maximum daily dose (MDD). Please be reminded that if a DMF holder does not know the MDD of the drug product, even the ICH Q3A qualification threshold and identification threshold cannot be set.

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# Poster#15: Establishing Impurity Acceptance Criteria As Part of Specifications for DMFs Based on Clinical Relevance

Presenter: Dr. Yongjun Gao

Topic: Case 4: Comparative impurity analysis

**Question**: The Case 4 slide suggests that an acceptance criterion may be supported by comparative impurity analysis for the proposed drug substance and the RLD. Does this suggestion mean to use the drug product that is RLD for comparison?

**Answer:** Yes. It is generally recommended that the comparative impurity analysis should be conducted using at least three batches of the DMF holder's drug substance and three batches of the RLD drug product .

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# Poster#15: Establishing Impurity Acceptance Criteria As Part of Specifications for DMFs Based on Clinical Relevance

Presenter: Dr. Yongjun Gao

Topic: Case 6: Acceptance criteria for metabolite impurities

**Question**: Why are the acceptance criteria of significant metabolites limited to the ICH qualification level? If the toxicology of a metabolite is established, the acceptance criterion should be higher than the qualification limit.

**Answer:** A limit higher than the qualification limit for a metabolite impurity may be acceptable, with appropriate justification. The justification should provide quantitative information (e.g., plasma levels of the metabolite in animals and humans at the maximum daily dose or the exposure levels in animals that equals or exceeds the proposed clinical exposure levels) to demonstrate that the systemic exposure is at such a level to qualify the proposed level of the impurity.

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# Poster#17: Communications with DMF Holders and Applicants throughout the DMF Lifecycle

Presenter: Fatima Sequeira

Topic: Advice about post approval API manufacturing site changes

Question: Our company is planning on transferring our API process to a second manufacturing site. What mechanisms are there for us to discuss our plans for the DMF amendment, with the FDA? This would include:

- The categorization of the change;
- The best approach to include information in the various DMF sections;
- The best approach to demonstrate equivalency of intermediates and the final drug substance.

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## Answer:

- First we recommend looking at the available FDA guidance on the topics and we refer you to:
  - ✓ Guidance for Industry: Changes to an Approved NDA or ANDA
  - ✓ Draft Guidance for Industry: Post-approval Changes to Drug Substances

- If, after looking at the available guidance you have questions about the appropriate content of a DMF amendment for supporting the change and the appropriate supplement filing category for the change, use informal communication by submitting an email to DMFOGD@FDA.HHS.GOV.

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## Answer:

- In your email remember to include:
  - ✓ A complete description of the change
  - ✓ Address and FEI number for any associated facilities
  - ✓ Proposed submission date of the DMF amendment

- This information is sufficient for us to offer advice on the supplement filing category (which you can share with your customers) and on information to include in the DMF amendment to document the change.

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# Poster#18: Teleconference

Presenter:  CDR Benjamin Danso

Topic: T-con Grant/Deny Decision

Question: In the event that a DMF holder receives a GRANT with written response to a teleconference request that they placed to the agency, does this mean that the DMF holder could still ask for a 30 minute telephone meeting with the agency?

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# Answer

A T-con GRANT with a written response from the agency serves two purposes.

- The written response is meant to provide the DMF holder with answers to the questions, in full or in part, submitted in the t-con request. DMF holders, upon receipt of the agency's written response, may consider that as a closure to their query if the written response provided them with enough clarity to move forward with answering the CR letter.
- On the other hand, if the DMF holder still sees the need to have a telephone conversation with the agency, the holder still has the opportunity to do so. At this point, the DMF holder should reach out to the RBPM and request that the meeting be scheduled.
- When proceeding with the T-con we recommend the holder use any information provided in a written response to make the 30-minute T-con as efficient as possible.

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# Poster # 19 : List of Relevant Quality Guidances & Common Deficiencies Observed During Drug Master File (DMF) Review

## Presenter: Sad Ahamed

Topic: List of Relevant Quality Guidances for DMF review

**Question# 1:**

As regards your poster on the deficiencies commonly observed in Section 3.2.S.3.2 of the DMF, you state that all the potential impurities that may be present in the API must be discussed. However, we have observed that FDA enquires about other impurities during CR Letters. Though the DMF holder discusses the potential impurities that he has actually observed during development and are consistently present in his process.

How can a DMF holder interpret/evaluate what other impurities need to be evaluated and discussed in the DMF other than those actually observed.

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Answer:

- DMF holder should include a discussion on potential and observed impurities from the quality perspective on a case by case basis i.e. based on synthetic scheme and manufacturing process. Discussion may include, process impurities including potential side products, potential contaminant due to solvents/reagent used in the manufacturing process, possible impurities due to competing reaction, impurities possible by the synthetic route particularly starting materials introduced late in the process or degradation impurities, discussion of the downstream analogs, along with supporting data and control strategies.

- If you receive a complete response/deficiency comment about an impurity that is not observed or likely cannot be formed from your route of synthesis and manufacturing process, then it is acceptable to respond that the impurity is not possible or likely, along with your scientific rationale and any supporting information such as analytical data or literature references.

- We refer you to ICH Q11 (that discuss use of risk assessment tools to better understand link between process and quality) and ICH M7 (ICH M7 section 5, which pertains directly to actual and potential impurities and hazard assessment expectations).

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**Question# 2:**

When does the Agency plan to finalize the 'Post approval Changes to Drug Substances' Draft guidance issued in Septmeber-2018? Again, it is recognized that this conference focuses on GDUFA- DMFs, but some of these guidances need to be finalized as one DMF may support multiple ANDAs (some of which could be under review).

**Answer:**

FDA has received public input from stakeholders regarding this draft guidance in comments submitted to the public docket. FDA will determine next steps based on our analysis of comments and revise the draft guidance as necessary. Please be advised that FDA's guidance documents, including draft guidances such as this, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

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**Question# 3:**

Is the submission of process validation mandatory or a new requirement? Historically validation information has not been submitted.

**Answer:**

FDA regulations describing current good manufacturing practice (CGMP) for finished pharmaceuticals are provided in 21 CFR parts 210 and 211.....Process validation is required, in both general and specific terms, by the CGMP regulations in parts 210 and 211. We refer you ICH Q7 “Good manufacturing practice for active pharmaceutical ingredients”. (Final, September 2016)

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**Question# 4:**

Does the statement “Caution: for manufacturing, processing, or repacking” need to be part of the product label, or can it be a separate label or sticker on the container?

**Answer:**

Yes, the caution statement need to be part of the product label which requires specific labeling on the package  such as "Caution: For manufacturing, processing, or repacking”. Information that goes on the label should be part of the label and not a sticker. You can be referred to ICH Q7: Good manufacturing practice for active pharmaceutical ingredients (Final, September 2016).

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# Thank You!

- Send questions regarding all posters and presentations 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.

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