U.S. FOOD & DRUG ADMINISTRATION

Presenter: Anita Tiwari

Topic: ICH Q11 Q&A, a Supporting Document for the Selection and Justification of Starting Materials

Question:

A well characterized small molecule drug substance (DS) was previously submitted in a Drug Master File (DMF) and is now being submitted as part of a new DMF with no change to the manufacturing process. Will the manufacturing process be assessed against the current ICH Q11 requirement for selecting starting material (SM)? Will there be a new starting material assessment performed?

Answer:

Yes. In a new Drug Master File (DMF), it is recommended to include justification for the regulatory starting material selection according to ICH Q11 general principles described in Section 5.1.1 and all the information related to the starting material(s) including upstream process (as applicable) should be included in Section 3.2.S.2.3.

Question:

Is the API manufacturer required to include the route of synthesis and impurity discussion/controls for the regulatory starting material in a Drug Master File?

Answer:

Yes. There may be several synthetic routes for the preparation of regulatory starting material whether it is commercially available, or custom made. Therefore, it is recommended that API manufacturer should include route of synthesis and discussion/controls of impurities including mutagenic impurities in the submission for a regulatory starting material procured from each supplier for better understanding of the process.

Question:

Should changes in the supplier/manufacturer of starting material (SM) be reported in the Drug Master File (DMF)?

Answer:

Yes. Changes in the supplier/manufacturer of starting material should be reported in the DMF. Please note that all the CMC information for the starting material procured from the proposed supplier should be included in the submission as applicable.

Question:

Why are raw materials like fumaric acid, malic acid or citric acid not considered regulatory starting materials and subject to a higher level of scrutiny?

Answer:

Fumaric acid, malic acid or citric acid are used as counter-ions with the drug substance in the process. USP-NF monographs are available for them. Therefore, they are not considered as regulatory starting materials. The specifications of these acids should be in line with the USP-NF monographs. However, please note that the USP-NF monograph is the minimum requirement. Since these acids are generally used in the final step to make salts, all plausible impurities should be controlled in the specifications.

Question:

Does a commercially available chemical need to be manufactured under cGMP to be acceptable as starting material (SM)?

Answer:

No. Please note that cGMP pathway starts from the first use of regulatory starting material in the drug substance manufacturing process. Therefore, commercially available chemical as SM is not required to be performed under cGMP. However, if API manufacturer performs purification of this material to control impurities, per ICH Q11 Q&A 5.14 they should include the purification step(s) of the commercially available chemical in the synthetic route in section 3.2.S.2.2 and perform under cGMP. They should provide the specifications of pre-purified material and purified material in the submission. Please note that purified material will still be considered as a starting material.

Question:

If a late-stage intermediate is referenced in a secondary Drug Master File (DMF) then can we refer to this intermediate as a starting material in the primary DMF and /or application?

Answer:

No. Late-stage intermediate in the primary DMF should be referred as intermediate not a starting material. Quite often we see this issue in the Drug Master File. You may outsource or procure this intermediate from different suppliers in the future. Also, there may not be enough cGMP steps in the drug substance manufacturing process. Therefore, late-stage intermediate in the primary DMF should be referred as intermediate not a starting material.

Question:

What is the difference between a "Starting Material" and a "Key Starting Material" or "Advanced Starting Material”?

Answer:

There is no difference between a "Starting Material" and a "Key Starting Material". They are same. However, there is not a term as "Advanced Starting Material". It should be referred to as intermediate in the DMF submission.

Thank You!

U.S. FOOD & DRUG ADMINISTRATION

Presenter: Hongbiao Liao

Topic: Regulatory Considerations for Impurity Qualification

Presenter: Hongbiao Liao
Topic: Regulatory Considerations for Impurity Qualification

Question: Does the FDA apply ICH Q3A for unknown impurities in peptide drug substances?

Answer: Peptides are excluded by ICH Q3A. We do not apply ICH Q3A identification threshold for any unspecified impurity of peptide drug substances. The limit for any unspecified impurities in peptides is determined on a case-by-case basis.

For certain highly purified synthetic peptide, any new impurities not observed in the RLD should not exceed 0.50%. Each of the new impurities present at above 0.10% should be identified and justified. You might refer to a draft guidance: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products.

Presenter: Hongbiao Liao
Topic: Regulatory Considerations for Impurity Qualification

Question: Drug substance manufacturer sets impurity limits per first drug product's MDD. Second drug product manufacturer wants to use the same drug substance but has a higher MDD. Should the drug substance meet the tighter requirements, or is the drug substance allowed for the second drug product?

Answer: If a DMF is intended to support multiple ANDAs with various MDDs, highest MDD should be selected for the calculation of identification and qualification thresholds per ICH Q3A.

In your case, in order to support the second drug product, the drug substance manufacturer should tighten the impurity limits to meet the tighter impurity requirements.

Presenter: Hongbiao Liao

Topic: Regulatory Considerations for Impurity Qualification

Question: Is full validation sufficient for in-house test method for organic impurities in drug substance or is an equivalency report also required between the in-house method and USP monograph method?

Answer: If USP monograph provides method for related substances, an alternative impurity test method should be fully validated. Equivalency studies should also be performed to demonstrate that the alternative method is equivalent or better than the USP method.

For the equivalency study, we need: A. The multiple batches which are tested by both USP method and alternative method to show the results are comparable. B. All USP specified impurities should be included in the equivalency study, unless it has been justified appropriately. For example, it is a process impurity and not possible in the manufacturing process.

Presenter: Hongbiao Liao

Topic: Regulatory Considerations for Impurity Qualification

Question: Is it necessary to perform elemental impurity assessment again for changes like raw material quantity optimization, batch size change, and equipment change?

Answer: It is case by case. Changes like raw material quantity optimization, batch size and equipment size changes are less likely to result in an adverse impact on elemental impurities.

However, elemental impurities can be potentially introduced into the drug substance from manufacturing equipment. The risk can be reduced through process understanding, equipment selection, equipment qualification and good manufacturing practice processes. In case of change of equipment type (e.g., from glass-lined reactor to alloy reactor), you might consider repeating risk assessment of elemental impurities.

U.S. FOOD & DRUG ADMINISTRATION

Presenter: Dr. Yongjun Gao

Topics:

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

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

Presenter: Dr. Yongjun Gao

Topic: General question

Question:

In this Poster, it is stated that the acceptance criterion for a specified impurity may be established at more than the ICH qualification threshold if available compendial limits are greater than the ICH qualification threshold. In this case, can you kindly guide us how to confirm whether higher limits are used for releasing API in marketed products?

Answer:

You may refer to publicly available information such as compendial monographs, scientific literature, FDA approved package inserts, and published FDA research and assessments.

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:

If there is no USP monograph for a drug product, the proposed limit for a specified impurity is more than ICH Q3B(R2) threshold wherein the RLD limit for this impurity is also more than the ICH limit. In this scenario, is it necessary to test both the RLD and ANDA products using the same analytical method for the side-by-side comparative impurity analysis?

Answer:

In general, the same analytical methods should be used for comparison of ANDA products with RLD.

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

Presenter: Dr. Yongjun Gao

Topic: Acceptance criteria for total impurities

Question:

What is the maximum limit for total impurities in a drug substance?

Answer:

FDA MAPP 5017.2 clearly addressed this question.

According to this MAPP, the acceptance criterion for total impurities excluding significant human metabolites, generally, should not exceed the summation of acceptance criteria for individual specified (identified and unidentified) impurities. The sum total of all impurity limits, including those for significant metabolites, should not exceed thresholds that may compromise product potency/assay through product expiry.

Poster#13: Evaluation of Elemental Impurities in Drug Substances

Presenter: Donglei Yu

Topic: Elemental Impurities

Question: This question is concerning the control of elemental impurities in drug products containing very low doses of drug substance (API). For a drug substance with an MDD of 50 µg/day, the limit for a class 1 elemental impurities, such as Cd or Pb, is very high (100,000 ppm):

Limit for Cd (or Pb) = PDE (µg/day) / MDD (g/day)
= 5 µg/day / 0.000050 g/day
= 100 000 ppm
= 10 % of drug substance

Can I use this high limit to justify the exclusion of the screening for elemental impurities in the drug substance?

Answer:

- No, we do not accept your justification of excluding screening for elemental impurities.

$$Concentration(\mu g / g) = \frac{PDE(\mu g / day)}{daily\ amount\ of\ drug\ \ product(g / day)} \qquad (1)$$

- If you use Option 2a, the maximum concentration is determined using the actual drug product daily intake, but not the MDD of the drug substance.

- When using the above formula to calculate the permitted concentration of an elemental impurity, we recommend Option 1 for drug products with daily intakes of no more than 10g.

How to Assess Elemental Impurities in a Drug Substance

- Elements need to be evaluated (*Table 5.1* in ICH Q3D)
- PDEs per Route of Administration (*Table A.2.1* in ICH Q3D)
- Converting PDEs to allowable concentration limits (Section 7 of ICH Q3D)

$$Concentration(\mu g / g) = \frac{PDE(\mu g / day)}{daily\ amount\ of\ drug\ product(g / day)}$$

Option 1, 10g/day

MDD of DS (MDD>10g/day) (You should work with ANDA applicant to set up limits)

- *ICH Q3D is a guidance for drug product. Drug substance is only one of the sources of elemental impurities in a drug product.*
- *We suggest the DMF holder work with the ANDA applicants to determine appropriate limits for elemental impurities.*

U.S. FOOD & DRUG ADMINISTRATION

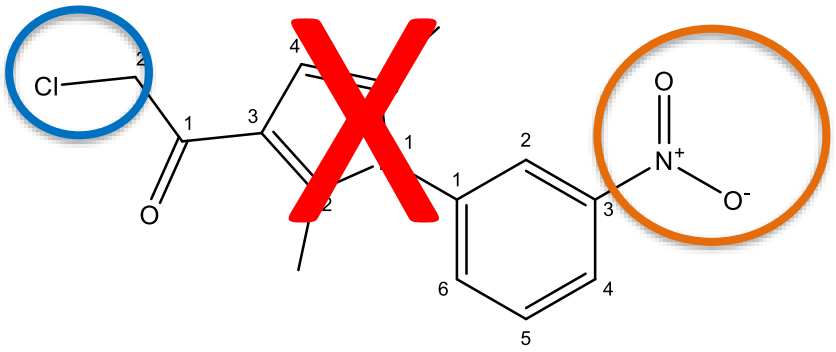
Presenter: Barbara Scott

Topics: ICH M7 Hazard Assessment and ICH M7 Main Guideline

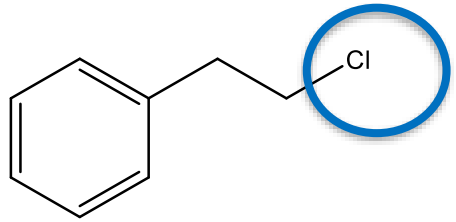
Presenter: Barbara Scott
Topic: Mono-functional Alkyl chloride

Question: Please define what is meant by “mono-functional alkyl chlorides” in Note 5 of the ICH M7 main guideline.

Answer: A mono-functional alkyl chloride is defined as a molecule containing only one alkyl chloride alerting functional group with no other alerting functional groups present.



Not a mono-functional alkyl chloride



mono-functional alkyl chloride

Presenter: Barbara Scott
Topic: Monofunctional alkyl chloride

Question: Are other mono-functional alkyl halides, for example mono-functional alkyl bromides, eligible for the 10-fold allowable increase in default TTC per Note 5 in the ICH M7 main guideline?

Answer:

No, the body of safety data that was reviewed by the ICH Expert Working Group was specific to the carcinogenic risk that monofunctional alkyl chlorides posed to the patient and is not applicable across other monofunctional alkyl halides. Please refer to the chapter by Brigo and Muller (reference 15) from Note 5 in the main guideline.

Presenter: Barbara Scott
Topic: Hazard Assessment

Question: You mentioned in your talk that visual inspection of a compound for structural alerts for classification purposes was not ICH M7 compliance. What does visual inspection here refer to? Could you elaborate?

Answer: Often times DMF holders will submit simple statements that "no structural alerts were identified" and there is no accompanying M7 compliant (Q)SAR report in the submission. In these cases, the Agency assumes that this statement is the result of 'visual inspection,' which is the comparison of the impurity structure against literature reports[1] that discuss structural classes associated with mutagenicity. Visual inspection can be useful as a preliminary screen for potential mutagens but (Q)SAR model predictions are needed for ICH M7 compliance as they provide a more accurate prediction of mutagenic potential. **Visual inspection is not M7 compliance.**

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[1] 1) Benigni and Bossa, 2011. Chem. Rev. 111, 2507-2536; 2) Müller et al., 2006. Regul. Toxicol. Pharmacol. 44, 198-211; 3) Enoch and Cronin, 2012. Mut. Res. 743, 10-19; 4) O'Donovan et al., 2011. Mut. Res. 724, 1-6.

Presenter: Barbara Scott

Topic: Hazard Assessment

Question: Can one use the AIs/PDEs listed in the ICH M7 addendum for structurally similar compounds? For example, benzyl chloride has an AI/PDE of 41 ug/day. Can one apply that limit for a structurally similar chemical like para-methyl benzyl chloride? Example is for illustrative purpose only.

Answer: The acceptable intakes in the ICH M7 Addendum apply to the impurity listed and are based on the analysis of appropriate positive carcinogenicity data as outlined in the compound specific monograph.

However, Section 7.B and Note 5 of ICH M7(R1) address the use of chemical similarity considerations in applying compound-specific AIs/PDEs to other compounds. Compound-specific calculations for acceptable intakes can be applied for impurities which are chemically similar to a known carcinogen compound class (class-specific acceptable intakes) provided that a rationale for chemical similarity and supporting data can be demonstrated. These justifications are consulted to the Safety Team in OGD and evaluated on a case-by-case basis.

Presenter: Barbara Scott
Topic: Multiple Potentially Mutagenic Impurities

Question: If there is more than 1 mutagenic impurity in API , do we need to include a combined limit for all impurities or can an individual limit be given?

Answer: Section 7 of ICH M7 states that when there are **three or more** Class 2 or Class 3 impurities specified in the drug substance specification, a limit for each individual impurity should be listed in the drug substance specification per the acceptable intakes provided in Table 2. Additionally, in this case, a limit for Total Mutagenic Impurities should be listed in the specification table per the acceptable intakes provided in Table 3.

As stated in the guidance, compound specific or class-related acceptable intakes and degradation products which form in the drug product are excluded from total mutagenic impurity limits.

Presenter: Barbara Scott
Topic: S9 Exemption

Question: Are cancer drugs generally exempt from ICH M7?

Answer: Drug products that are intended to treat* advanced cancer as defined by ICH S9 are out of scope for ICH M7. However, Appendix 1 of ICH M7 has a caveat to consider should an approved existing drug product associated with an advanced cancer indication be registered for use in a non-life threatening indication. In this case, since the patient population and acceptable cancer risk have changed, the previously approved control strategy and limits would require re-evaluation for both the drug substance and the drug product.

*Per ICH S9 drug products used to prevent cancer, treatment of symptoms of cancer or side effects of chemotherapy are in scope of ICH M7

Presenter: Barbara Scott
Topic: Hazard Assessment

Question: If the impurity listed in USP monograph is a probable genotoxic based on (Q)SAR, can we go ahead with USP limit or do we need to control based on TTC limit?

Answer: USP monograph impurities, that after a hazard assessment is performed, are predicted positive by (Q)SAR should be further addressed as a Class 3 impurity. An Ames test can be conducted and if negative the impurity is downgraded to Class 5 (USP limit would apply). If the Ames test is positive, an in-vivo gene mutation study can be performed and if negative the impurity is downgraded to Class 5 (USP limit would apply). Otherwise, the class 3 impurity can be controlled by any of the four options outlined in the ICH M7 guidance.

We further recommend that you petition the USP for a monograph revision to have the impurity limit tightened based on a positive outcome of the Ames or in-vivo gene mutation studies.

Presenter: Barbara Scott
Topic: MDD/Acceptable Intake

Question: In cases where the intended drug product labeling may be unclear, does the Agency have a mechanism for industry to request assistance for determination of the MDD/acceptable intake prior to filing a DMF or ANDA?

Answer:

DMF holders and ANDA Applicants should use the controlled correspondence communication mechanism for questions regarding MDD/acceptable intake information. See Controlled Correspondence Related to Generic Drug Development Draft Guidance for Industry:

https://www.fda.gov/media/109232/download

U.S. FOOD & DRUG ADMINISTRATION

Presenter: David Green

Topics: Control of a PMI tested below 30% TTC and (Q)SAR negative but known carcinogenic impurity

Presenter: David Green

Topic: PMI below 30% TTC Limit in 3 Commercial Scale Batches

Question:

If a manufacturer shows that the levels of a potential mutagenic impurity are consistently 30% below the TTC limit in three commercial scale batches of the API, is this sufficient evidence to omit routine control of the mutagenic impurity from the release specifications?

Answer:

No. Batch data alone demonstrating that a potential mutagenic impurity is consistently <30% TTC is not sufficient to justify no testing of that impurity. Control options 1, 2, or 3 should be utilized to test either at release or upstream in the process.

- Per ICH M7 if the Option 3 control strategy (upstream control) is chosen, then two conditions should be met to justify this control strategy:
  - Spike/ purge experiment at the proposed limit from laboratory scale experiments and where necessary supported by data from pilot scale or commercial scale batches.
  - Data from multiple batches which is consistently <30% TTC.

However, if there is negligible risk of the impurity to be present in the drug substance, an Option 4 control strategy may be considered with appropriate justification.

Presenter: David Green
Topic: (Q)SAR negative but known carcinogenic impurity

Question:
If an impurity is found non-mutagenic by (Q)SAR but is a known carcinogen then what would be the classification for such an impurity? Does this carcinogenic impurity need to be controlled / evaluated at the TTC level?

Answer:
Carcinogenic impurities that are negative in the bacterial reverse mutation assay or by (Q)SAR analysis do not have a DNA reactive mechanism of carcinogenicity and therefore are not in the scope of the ICH M7 guidance. The DMF holder should refer to ICH Q3A Appendix 3 and the accompanying notes for control of this impurity.

U.S. FOOD & DRUG ADMINISTRATION

Presenter: Naomi L. Kruhlak, Ph.D.

Topic: ICH M7 (Q)SAR

Follow-Up Q&As to SBIA DMF and Drug Substance Workshop
April 9, 2021

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Question 1: Acceptable Software

What software are recommended to perform an ICH M7 (Q)SAR analysis?

Answer: The agency is unable to recommend specific software. However, general attributes of suitable models can be provided. Suitable models for ICH M7 (Q)SAR analyses are those that:

a) Are updated frequently (every 1-3 years), where those updates include addition of new training set chemicals and mutagenicity data. A model that has an updated software interface, but a training set that pre-dates ICH M7's finalization in 2014, is not suitable. Information on the age of the model and its training set can be obtained from the model's (Q)SAR Model Reporting Format (QMRF) document. Models that are frequently updated by the developer are recommended as they generate predictions based on the most current information available.

Question 1: Acceptable Software, cont'd

b) Provide predictions in the form of alerting or mitigating sub-structural features. This provides mechanistic insight into the predictions, thereby facilitating the application of expert knowledge.
c) Use training sets that are visible to the user. This increases transparency in the predictions and facilitates the application of expert knowledge, where training set structures supporting a prediction can be reviewed by the user for relevance. In short, it is difficult to confirm or refute a prediction is if it unclear how the model arrived at that prediction (i.e., it functions as a "black box").

The software the agency uses for in-house (Q)SAR analyses is highlighted in the red box on Slide 8 of my March 3rd presentation.

Question 2: Testing Laboratory

If we use a laboratory to make (Q)SAR determinations for a DMF, does the (Q)SAR laboratory need to be certified?

Answer: No, the laboratory performing the (Q)SAR analysis does not need to be certified. It is not considered a testing facility for fee-related purposes.

Question 3: Model Output Files

Are (Q)SAR model output files required in a submission?

Answer: No, they are not required, but they are preferred. They improve review efficiency by providing unambiguous evidence of a prediction and its supporting data. In the absence of model output files, predictions may need to be re-run by the agency to confirm conclusions, increasing review time.

Question 4: Purged Impurities

Do impurities that are predicted to be purged from the process, e.g., using Mirabilis, need (Q)SAR assessment?

Answer: Yes, all actual and potential impurities most likely to arise during the synthesis, purification and storage of the drug substance should be analyzed by (Q)SAR regardless of whether they are expected to be purged.

Question 5: Re-running Predictions

How often do we need to update the (Q)SAR information in the DMF? If FDA considers a (Q)SAR prediction shelf-life of 2 years (as rule of thumb), then are DMF holders expected to re-assess API impurities for ICH M7 every 2 years?

Answer: Once a DMF application is found adequate to support a referencing ANDA, (Q)SAR predictions are not expected to be re-run unless a specific cause for concern is identified.

A specific cause for concern could be positive Ames data that becomes available for an impurity that was previously classified as negative (Class 5). In such a case, only the specific impurity impacted would need to be re-evaluated.

Question 6: Shared Alerts

A drug substance itself contains an alerting structure (aromatic amine). It gives an Ames positive alert in (Q)SAR, but it is known that it is not genotoxic/mutagenic. Its process impurity has the same structure, except that it has an aromatic nitro instead of the aromatic amine. How should we evaluate this nitro impurity?

Answer: If the impurity had contained an aromatic amine in the same chemical environment as in the empirically negative API structure, the negative Ames data from the API could be used to dismiss the structural alert in the impurity. The impurity would then be re-assigned from Class 3 to Class 4 through the application of expert knowledge.

Question 6: Shared Alerts, cont'd

However, an aromatic nitro group is a different alert than an aromatic amine.

An aromatic nitro compound is more likely to be mutagenic than its corresponding aromatic amine.

Therefore, the negative API data cannot be used to dismiss the aromatic nitro structural alert in the impurity. However, data from other aromatic nitro compounds containing the alert in the same chemical environment may be used to confirm or refute the impurity prediction.

Question 7: Reagents

Does the agency require hazard assessment of all reagents as well as related impurities?

Answer: Yes, the agency requires assessment of all reagents and impurities. For reagents and impurities where Ames data are unavailable, a (Q)SAR prediction should be used to assess their mutagenic potential. This does not include solvents, which are covered under ICH Q3C.

Thanks!

Safety Evaluation of Drug Substance Impurities in Generics

Chanchal Gupta, Ph.D.
Pharmacology/Toxicology Reviewer
Division of Clinical Review (DCR)
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)
CDER | U.S. FDA

SBIA DMF Workshop Follow-Up Q&A Webinar – April 9, 2021

Presenter: Chanchal Gupta
Topic: Impurity qualification – metabolites

Question:

- If an impurity is a metabolite of the drug substance, is it considered qualified for safety?

Answer:

- Safety justifications for impurities which are considered metabolites of the drug substance should include both qualitative and quantitative information to qualify the impurity at the proposed level.

- Quantitative information such as plasma levels of the metabolite in animals and/or humans at the maximum daily dose that equals or exceeds the proposed clinical exposure levels should be provided to demonstrate the relevant systemic exposure to the impurity.

- Reference: Good ANDA Submission Practices Guidance for Industry

Presenter: Chanchal Gupta
Topic: Duration of use

Question:

- Can antibiotics be considered as drugs for short-term duration of use?

Answer:

- Duration of use of a drug product should be determined based on the total number of dosing days in a patient's lifetime.
- Certain antibiotics may be used repeatedly over the lifetime of a patient to treat multiple disease episodes.
- Hence, duration of use of an antibiotic drug product should be determined, considering its clinical use over the lifetime of a patient. Refer to the reference listed drug (RLD) labeling for context of use of the drug product.
- Reference: M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk

Presenter: Chanchal Gupta
Topic: DMF shared between multiple ANDAs

Question:

- If a DMF supports several ANDAs, how are impurity limits in a DMF qualified for safety?

Answer:

- Impurity limits in a DMF are qualified with respect to the referencing application*.

- DMF holders should consider the context of use i.e., maximum daily dose (MDD), duration of use, route of administration, and patient population of all referencing applications supported by the given DMF for qualification of drug substance-related impurities.

- Safety qualification should include genotoxicity and general safety assessment.

* Referencing application refers to the Abbreviated New Drug Application (ANDA) and/or the New Drug Application (NDA), supported by the Drug Master File (DMF)

Answer (continued):

- When setting control limits for mutagenic impurities, consider the duration of use of the product and the MDD for chronic use (highest dose of the drug administered amongst all referencing applications). If the proposed limit exceeds the threshold of toxicological concern (TTC), a mutagenicity assessment is warranted.
- When setting limits for non-mutagenic impurities, the maximum possible daily dose is used to determine the qualification threshold (QT). If the proposed limit exceeds the QT, a general safety assessment is warranted.
- References: M7(R1), Q3A, and ANDAs: Impurities in Drug Substances

U.S. FOOD & DRUG ADMINISTRATION

Presenter: Deborah F Johnson, Ph.D.

Topic: Nitrosamines

Presenter: Deborah Johnson
Topic: Nitrosamines- control

Question: Are the chemicals precursors and DMFs for chemical precursors for radiopharmaceuticals (PET, SPECT) in the scope of the FDA Nitrosamine guidance?

Question: Should the Nitrosamine evaluation be carried out for non-synthetic API?

Question: Does the FDA NDMA guidance only apply to small chemical molecules, but NOT biologics and vaccines?

Answer:

- If the radiopharmaceuticals are chemically synthesized, then they are covered in the guidance scope. A risk assessment of the synthetic route, starting materials and raw materials should be performed.
- The answer for non-synthetic API is “no, unless there is reason to suspect that the product contains nitrosamines (e.g., suspected contamination, synthetic step that places the product at risk, vulnerable API and process steps).”
- For biologics and vaccines, the guidance applies to chemically synthesized drugs, which includes any drug (API or drug product) with a chemically synthesized structure, or where the manufacturing process is at risk to nitrosamine contamination due to other factors. If the biologics have chemically synthesized fragments or the process which has risk of nitrosamines, the guidance applies. The guidance does not include biologics that are not chemically synthesized.

Presenter: Deborah Johnson
Topic: Nitrosamines- control

Question: What level of testing and controls for nitrosamines are expected for components of container closure systems, for example rubber stoppers?

Answer:

- The level of control should be commensurate with risk that nitrosamines from the packaging could migrate into the API. The FDA: Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics Section III.B.b “Compatibility” and Table 2 shows the degree of concern with the type of drug product and the container closure components. Liquid formulations have the highest degree of concern with compatibility as they are the most likely to be at risk for leaching and/or extracting impurities from container components. Likewise, a liquid API would present a higher risk of contamination from container closure components than a solid API.

Presenter: Deborah Johnson
Topic: Nitrosamines- control

Question: How many batches will be enough to support results for nitrosamines?

Answer:

- The number of batches should be guided by the understanding of the risk. Nitrosamine formation in an API may be completely unrelated to the actual chemistry being used to form the API molecule. Side reactions between impurities and/or reagents have often been responsible for nitrosamine formation. With a side reaction it may be difficult to predict how much nitrosamine will form each time. Without an understanding of how much nitrosamine is being formed it is difficult to discuss a purge strategy. Enough batches should be tested to fully justify any proposed control strategy. In general, $n \geq 3$ would be expected.

Presenter: Deborah Johnson
Topic: Nitrosamines- control

Question: What is the scientific rationale behind the statement “Theoretical purge factor calculations may overestimate purging factor of the process.”

Answer:

- Theoretical purge calculations are designed to be conservative. However, the purge factors (i.e., 1, 10, 100, 1000) should be based on scientific evidence. In some cases, firms assumed that NDMA and NDEA were “completely miscible” in water and therefore would be adequately removed from the process due to the high number of aqueous work ups and yet the API was contaminated with nitrosamines. Solubility studies discovered that while NDMA and NDEA were indeed “water miscible” they were also very highly soluble in organic solvents. The aqueous wash steps were much less effective than predicted at removing the nitrosamine impurities.

Presenter: Deborah Johnson
Topic: Nitrosamines- control

Question: The guidance recommends that the LOQ for all nitrosamines be <0.03 ppm and that routine testing be carried out when impurities are detected above the LOQ. Does above statement mean that the decision on the need for routine testing should be based on the testing results of <0.03 ppm or > 0.03 ppm value instead of calculated acceptable limit based on AI of specific nitrosamine?

Answer:

- The FDA Nitrosamine guidance does state that the LOQ of the methods used for monitoring nitrosamines should have an LOQ of NMT 0.03 ppm. In general, the LOQ of a method should have a S/N of >10 and is determined experimentally. However, the Agency felt it was necessary to recommend an LOQ of NMT 0.03 ppm due in part to the large number of drug products that have MDDs >100 mg.
- An LOQ of NMT 0.03 ppm was also recommended because if there are more than one nitrosamine listed in the specification, then there must also be a test for "total nitrosamine" with an AI of 26.5 ng/day. In order to calculate the total nitrosamine level the LOQ for each nitrosamine may need to be significantly lower than would required for the limit based on the AI of the nitrosamine alone.
- In the case where the MDD of the drug product is low, the nitrosamine limits may be high enough to justify an LOQ >0.03 ppm.
- The guidance states that routine testing should be incorporated when nitrosamines are detected at a level greater than the LOQ of 0.03 ppm. If the MDD is quite low an argument could be presented to justify using a higher LOQ as the testing/non-testing threshold especially if that LOQ is 1-10% of the allowable limit.

Presenter: Madhusudhan Gowravaram, Ph.D.

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

Presenter: Madhusudhan Gowravaram
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Question:
What is the definition of a critical intermediate?

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Question:
What is the definition of a critical intermediate?

Answer:
A critical intermediate is an intermediate whose manufacturing process is deemed so important to the quality of the finished API that the manufacturing site needs to be part of the facility evaluation for the referencing application.
I recommend you listen to the “Drug Substance Facilities – Hidden and Critical Intermediate Sites” presentation given during the March 3-4, 2021 DMF workshop for additional information.

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Question:
Whose responsibility is it to inform the ANDA applicant of a secondary DMF being used to source a critical intermediate?

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Question:
Whose responsibility is it to inform the ANDA applicant of a secondary DMF being used to source a critical intermediate?

Answer:
We recommend that the primary DMF holder inform all referencing ANDA applicants of critical intermediates contained in a secondary DMF so that the facilities can be included in the applicant's 356h form. If this information is not provided to the Applicant, the Agency cannot convey the status of such facilities and the ANDA facility assessment may be delayed.

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Question:

(i) If an ANDA holder decides not to list a secondary DMF of critical intermediate on the 356h form, then does FDA ask the ANDA applicant to include it?

(ii) If yes, when does such a query happen? Would it be asked during RTR review cycle or during scientific review cycle?

(iii) What are the factors to be considered for deciding whether a secondary DMF supporting an intermediate is needed to be listed in the ANDA 356h form?

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Question:

(i) If an ANDA holder decides not to list a secondary DMF of critical intermediate on the 356h form, then does FDA ask the ANDA applicant to include it?

(ii) If yes, when does such a query happen? Would it be asked during RTR review cycle or during scientific review cycle?

(iii) What are the factors to be considered for deciding whether a secondary DMF supporting an intermediate is needed to be listed in the ANDA 356h form?

Answer:

(i) If the critical intermediate facility of the secondary DMF is not listed in the referring application, an IR letter will be issued to the ANDA applicant to contact the primary DMF holder regarding missing critical intermediate facilities of the secondary DMF.

(ii) The IR is issued after the application is found acceptable for filing when these discrepancies are discovered during the TCIR process. In some circumstances these facilities are discovered during the full scientific review of the DMF, and a communication will be issued to the applicant in an IR or CR, as appropriate.

(iii) Please listen to the “Drug Substance Facilities – Hidden and Critical Intermediate Sites” presentation given during the March 3-4, 2021 DMF workshop for the factors considered in determining the criticality of intermediates including secondary DMF sites.

U.S. FOOD & DRUG ADMINISTRATION

Presenter: David Amspacher

Topics: Process Validation

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Topic: Process Validation

Question:

As process validation is often not completed at time of DMF review, is it acceptable to provide a commitment to complete process validation and submit process validation summary in response to deficiencies raised during completeness assessment (incomplete comments letter) or CMC quality review (complete response letter)?

Answer:

- One thing to note is that the guidance states before any batch from a process is commercially distributed a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process. You must do the validation before any commercial distribution. It is possible to submit a DMF without validation data but the guidance notes that aspects of drug substances and manufacturing processes that are critical to product quality should be determined and control strategies justified. This is the reason we ask for your validation data, because we use it to justify the limits in your process for in-process testing and impurities.

Presenter: David Amspacher
Topic: Process Validation

Question:

Should both the process validation protocol and report be submitted in the DMF or is just the process validation report sufficient?

Answer:

The information that we use to justify the specifications in your process during our assessment is in the process validation report, so this is the most important thing to provide. All the process validation protocol information can be kept onsite.

U.S. FOOD & DRUG ADMINISTRATION

Presenter: Xinghua Wu

Topics: Common Deficiencies Related to LC and GC Methods in Type II DMFs

Question 1: Could you explain the difference between a “Spiked drug substance sample” and a “Simulated drug substance sample” on the slide 17 and how a suitable simulated sample is selected or designed, in order to study the extraction efficiency of the (genotoxic) impurity from a poorly dissolved drug substance (for the method validation)?

Answer:

- Difference
  - Spiked sample – The genotoxic impurities (GTIs) are in solution before being spiked to the drug substance
  - Simulated sample – The GTIs that are homogenously mixed with the drug substance are in solid form
- Preparation of a simulated sample
  - Prepare a homogenous solution of API containing the GTIs at the desired levels
  - Remove the solvent completely to provide a simulated sample in solid form
    - An extremely low level of the GTIs in the sample can be easily prepared
    - Homogeneity is achievable in comparison to dry blending

Question 2: What are considerations to the forced degradation studies from scientific perspectives?

Answer:

- Degradation within 5-20% is recommended if achievable
- Mass imbalance within the variation range of assay is acceptable
- Mass imbalance should be explored, and an explanation should be provided.
  - Non-UV absorbing degradants or different UV responses of degradants
  - Volatile degradants
  - Degradant(s) retained on the column
  - Degradant(s) co-eluting with the API
- An under stressed sample may not provide adequate data for assessment while an overly stressed sample may contain a large amount of secondary degradation products
- Forced degradation study is optional when adopting USP monograph methods.

Reference: *FDA Perspectives: Scientific Considerations of Forced Degradation Studies in ANDA Submissions*, Pharmaceutical Technology, 2012, 36:73-80

Question 3: While calculating the %RSD as per USP <621>, is it always using the upper limit as the B value? Does USP <621> apply to other methods such as LC-RI (LC-Refractive Index detector) for assay determination?

Answer:

- From an analytical chemistry perspective, the upper limit of the assay reflects the typical analytical error while the lower limit involves other objective factors such as water content, residual solvent content, organic and inorganic impurities, etc. Thus, the calculation of %RSD should be based on the upper limit of assay.

- We suggest you to directly contact USP regarding questions related to USP<621>. For some chromatography methods that can not meet USP<621>, justification should be provided in the DMF submission, and the proposed system suitability acceptance criteria should be reasonable based on the range of assay.

Question 4: Does the agency recommend the exact same HPLC column used by USP when adopting the USP monograph method? If a USP method is not working (for determination of related substances), how can equivalency be demonstrated?

Answer:

- It is not agency's position to recommend if the firms should use the exact same USP column when adopting a USP method. Using a different column with the same stationary phase is acceptable as long as the column equivalency has been demonstrated.
- In case the USP method is not suitable due to a different impurity profile
  - The firm can either demonstrate its in-house method is superior to the USP method
  - Or develop and validate a secondary method to quantify the impurities that can not be solved by the USP method

Question 5: We have an Assay and Related Substances all-in-one method. We had validated the linearity from LOQ to 120% of assay. Why are we requested to validate the linearity from LOQ to 120% of the spec limit (LOQ-0.12%) using the API? How might changing the injection volume affect RRF (Slide#7, Case 1)?

Answer:

- The reference standard of API is used to quantify individual unspecified impurities assuming they have the same UV response. In this case, the API reference standard is deemed an external standard of the impurity as well. Thus, validation of the linearity from LOQ to 120% of the spec limit using the API is needed. In addition, the slope of the linearity curve in the low concentration range (LOQ-0.12%) may be different from that in the high concentration range (80-120%).
- Increase of the injection volume will increase the concentration of analytes when the eluent pass through the cell of the UV detector. When the concentration of an analyte (API) is too high,
  - The previously validated linearity slope for API may change
  - Or the API peak could be saturated, and the UV response will not be proportional to the corresponding concentration anymore. Therefore, the previously established RRF may not be applicable.

Question 6: Are tailing factor and theoretical plates for system suitability of the test solution of API peak in the related substances test required?

Answer:

- It is case by case. Tailing factor is recommended when the peak tailing of API is significant, or the impurity peaks are close to the API main peak, especially for peaks on the tail of API peak.
- As per USP<621>

  The parameters *k*, *N (Number of theoretical plates)*, *r*, and r_G were developed for isothermal GC separations and isocratic HPLC separations. Because these terms are thermodynamic parameters, they are only valid for separations made at a constant temperature, mobile phase composition, and flow rate. However, for separations made with a temperature program or solvent gradient, these parameters may be used simply as comparative means to ensure that adequate chromatographic conditions exist to perform the methods as intended in the monographs.

Question 7: If you know the residual solvents in the drug substance based on the route of synthesis, can we develop and validate an in-house method instead of USP <467> chapter ?

Answer:

- Yes. A firm always can develop and validate its own residual solvent method based on its synthetic route.

Question 8: Is validation/verification of USP method for a Differential Scanning Calorimetry (DSC) test required?

Answers:

- We refer you to USP<1226>

> Verification is not required for basic compendial test procedures that are routinely performed unless there is an indication that the compendial procedure is not appropriate for the article under test. Examples of basic compendial procedures include, but are not limited to, loss on drying, residue on ignition, various wet chemical procedures such as acid value, and simple instrumental determinations such as pH measurements. However, for the application of already established routine procedures to compendial articles tested for the first time, it is recommended that consideration be given to any new or different sample handling or solution preparation requirements.

- However, if the DSC is used for quantitation purpose, validation of the method is required.

U.S. FOOD & DRUG ADMINISTRATION

Presenter: Wei Liu

Topics: Common CMC Issues in Type II DMFs

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Topic: Common CMC Issues in Type II DMFs

Question: In the event that a monograph is issued following the submission of a DMF, what is the expectation of the FDA for a manufacturer to do a retrospective assessment?

Answer: The basic principle is that the drug substance's specifications in the DMF need to be updated to comply with USP monograph requirements as appropriate.

- Impurities listed in the USP monograph should be controlled per USP requirements, unless justified appropriately.
  - Impurities that are listed in the USP but cannot be formed in your manufacturing process do not need to be included in the specification, but a footnote should be added to the specification and COA that states the impurity cannot be formed.

Answer (cont'd)

- If your original analytical methods are used for assay and/or impurities and they are different from USP compendial method, a method equivalency study should be established between your method and compendial methods.
  - All specified impurities in USP should be included in the method equivalency study or justify its exclusion appropriately.
  - In case of a dispute, the USP method will be the method of resolution.
- If original analytical methods for assay and/or impurities are changed to compendial methods, the method verification for the compendial method should be provided.
  - If an impurity is included in your drug substance specification but not in the USP impurity profile, it should be demonstrated that this impurity is still controlled appropriately after the method changes.

Presenter: Wei Liu
Topic: Common CMC Issues in Type II DMFs

Question: If the drug substance specification is updated during the DMF/ANDA review cycle according to the Agency's review comments, could you please give an idea that how the DMF holder should present the stability data summary in section 3.2.S.7?

Answer: If the drug substance specification updates include the stability indicating tests, the drug substance stability specification in S.7 needs to be updated accordingly.

- When the stability study is still on-going and the retest period for the drug substance is proposed tentatively based on available stability data, the stability data for future time points need to be tested per updated stability specification for on-going stability batches.
- When the stability study is completed and the retest period for the drug substance has been established:
  - The data should be provided to demonstrate the drug substance at the end of retest period meet all requirements in the updated stability specification.
  - All future stability data, such as annual batches, needs to be tested per updated stability specification.

Presenter: Wei Liu
Topic: Common CMC Issues in Type II DMFs

Question: A critical intermediate is planned to be purchased from two vendors. The vendor #1 uses the starting material A, while the vendor #2 uses the starting materials B and C to get the same critical intermediate. Is it possible to have both intermediate manufacturers with almost the same route of synthesis in one DMF?

Answer:

- According to guidance for industry *Completeness Assessment for Type II API DMFs Under GDUFA,* the Type II API DMFs intended for reference in a generic drug submission that are subject to the DMF fee under GDUFA may only contain a single drug substance manufacturing process.

- The single drug substance manufacturing process means the same starting materials and intermediates with minor variations being allowed in solvents and raw materials as long as the type of chemical transformation in each step is unchanged.