Change in API Supplier: Drug Substance Quality Tips

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Pre-approval Changes to Drug Substances

- Guidance for Industry published in December 2000 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/alternate-source-active-pharmaceutical-ingredient-pending-andas)
- Focuses on the use of alternate sources of the active pharmaceutical ingredients (API) in unapproved abbreviated new drug applications (ANDAs)
- To substitute an alternative source for the API, the following circumstances should exist:
  - The original API source is not being withdrawn due to deficiencies specifically relating to that API
  - The previous bioequivalence (test) batches and bioequivalence studies were acceptable
  - The specifications of the alternate source API are essentially the same as the original source API
- Applicants should submit an amendment to their pending application requesting the withdrawal of the primary API supplier with the supporting information to add the new supplier just as is expected for any supplier of an API

Post-approval Changes to Drug Substances

- Guidance for Industry published in April 2004 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/changes-approved-nda-or-anda)
- Draft Guidance for Industry published in September 2018 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-changes-drug-substances-guidance-industry)
  - Focuses on changes to drug substance manufacturing during the drug product application's postapproval period
  - Addresses how the risk of changes to the drug substance should be assessed
  - Includes recommendations regarding the documentation needed to support changes

Scope

- Applies to synthetic drug substances and the synthetic steps involved in preparing semisynthetic drug substances
- Covers the following changes:
  - Facility, scale, and equipment changes associated with all steps of drug substance manufacturing
  - Specification changes to starting materials, raw materials, intermediates, and the unfinished and final drug substance
  - Synthetic manufacturing process changes
  - Changes to the source of the drug substance
  - Changes to the container closure system for the drug substance

Facility Change Quality Tips

- A change from one drug substance manufacturer to another is considered a change in the source of the drug substance, not a change of facility
- Hidden Facilities: The recommended facilities that are in the DMF but do not appear on the NDA/ANDA 356h form are referred as hidden facilities
  - The following facilities in DMF are recommended to be included in NDA/ANDA 356h form. We recommend that these are listed under 3.2.S.2.1 in DMF:
    - Final drug substance manufacturing, micronization, sterilization and testing sites that are proposed to be involved in the disposition of commercial product
    - Sites for intermediates addressed by ICH Q7: Critical Intermediate is an intermediate whose manufacturing process is deemed so important to quality of the finished API that the manufacturing site needs to be part of the facility evaluation for the referencing application. Determination is made on a case-by-case basis using principles as outlined in ICH Q11 as well as the supporting data
    - Facilities used for storing or warehousing drug substance prior to a disposition decision, including that solely store the stability samples
  - Communicate all required facilities and their responsibilities **early** to NDA/ANDA applicant(s).
    - The Agency considers all facilities that are listed in a DMF applicable to the referencing NDA/ANDA unless explicitly stated in the DMF LOA that only certain facilities will be used.

If a hidden facility is identified, the following comment will be sent to A/NDA applicant:

There is a facility (e.g., DS manufacturing, intermediate, or release/stability testing sites) that is included in DMF XXXXX for [DMF subject] that was not listed in your application (i.e., Form FDA 356h and/or in Section 3.2.S.2.1). ***Please note that the Agency cannot provide to you the status of facilities not listed in your application.*** *Please contact your DMF holder to identify and resolve any discrepancies and clarify which DMF related facilities support your application. We recommend that the DMF related facilities supporting your application be added to your Form FDA 356h and in Section 3.2.S.2.1. If only a subset of the facilities in the DMF will be referenced by your application to support commercial manufacturing and/or testing, your LOA should specify those facilities. Absent this specificity, the Agency intends to assume that all facilities listed in a DMF support your application.* ***Note, there may be an extension of the performance goal date if any facilities have been added to the DMF since the last application assessment cycle.***

Specification Change Quality Tips

- Impurities that are listed in the compendium but cannot be formed in the manufacturing process do not need to be included in the specification; however, a footnote should be added to the specification and COA of the final drug substance that states that the impurity cannot be formed
- If the original analytical procedures are changed to compendial methods, the method verification for the compendial methods should be provided
- If an impurity is included in the original specification but not in the compendial impurity profile, it should be demonstrated that this impurity is controlled appropriately. A method validation report showing that the analytical procedure is appropriate for the noncompendial impurity should be provided
- If in-house methods are used for assay and/or related substances, method equivalency should be established between the in-house and compendial methods. All compendial-specified impurities should be included in the method equivalency study or justify its exclusion, if appropriate
  - We recommend using a crude API sample or a sample spiked with specified impurities at the specification limits for such method equivalency demonstration

Manufacturing Process Changes

Changes in route of synthesis are considered to have a moderate to high potential to adversely affect the impurity profile of the drug substance. The manufacturing process should be validated using the new route of synthesis. Impurity carryover studies and spike/purge studies should be conducted as appropriate. Control of mutagenic impurities in or expected to be in the final drug substance should be evaluated according to ICH M7 (section 4.1).

Assessment of Risk

- Any modification to drug substance manufacturing carries some risk of causing an adverse impact on quality
- Each drug substance manufacturer should assess the particular proposed modification to their drug substance to determine the risk associated with the change
  - Certain modifications (e.g., equipment changes) are viewed as less likely to result in an adverse impact than others (e.g., changes in the synthetic route)
  - Late-stage changes in the drug substance manufacturing process are generally viewed as more likely to have an adverse impact on the quality of the drug substance and, consequently, on the drug product

Assessment of Risk

Central Principle: a change in the drug substance manufacturing process can be adequately assessed by comparing three consecutive pilot or commercial scale batches of pre- and post- modification material

Evaluation may include but is not limited to:

- A comparison of impurities in pre- and post-modification intermediates, the unfinished drug substance, and/or the drug substance
- A comparison of the drug substance's physical properties before and after modification
- Drug substance stability data

Impurity Profile Evaluation

If the impurity profile of an isolated material (i.e., isolated intermediate, unfinished drug substance, or drug substance) following the change is equivalent to that of pre-change material, the drug substance's impurity profile is considered unaffected by the modification.

- Determine the stage in the manufacturing process at which impurities should be evaluated.
- Determine levels of existing and new organic impurities (ICH Q3A), residual solvents (ICH Q3C) and inorganic substances (ICH Q3D).
- Determine the potential for the formation of mutagenic and unusually toxic impurities, including nitrosamines (ICH M7, FDA's Guidance: Control of Nitrosamine Impurities in Human Drugs).
- Establish the adequacy of the analytical procedures used for the above purposes.

Impurity Profile Evaluation

If the manufacturing modification occurs at an upstream step before the final intermediate is produced, and equivalence cannot be demonstrated for the intermediate isolated immediately following the change, the impurity search should be extended to the next downstream intermediate.

The impurity search should also be expanded to include appropriate downstream impurities that may be formed during the manufacturing process. The evaluation process should be repeated on downstream intermediates up to and including the drug substance, if necessary.

DMF Prior Assessment

- The reauthorization of the Generic Drug User Fee Amendments (GDUFA) III program features a number of enhancements include a mechanism to enable assessment of DMFs in advance of certain ANDA and prior approval supplement (PAS) submissions.
- Pursuant to commitments under GDUFA III, FDA issued a draft guidance for industry entitled "Review of Drug Master Files in Advance of Certain ANDA Submissions Under GDUFA."
- Describes instances when an early assessment, or "DMF prior assessment," could be requested by a DMF holder and the circumstances under which FDA would commence an early assessment of Type II API DMFs 6 months prior to an ANDA or PAS submission referencing the DMF.
- Provides recommendations for such DMF holders when making a request

RECOMMENDED CONTENT FOR A PRIOR ASSESSMENT REQUEST

1. Statement that the submission is a "GDUFA DMF Prior Assessment Request."[19]

2. A clear statement that the DMF holder is granting FDA permission to perform a substantive scientific review of the DMF.

3. Statement indicating the type of ANDA submission that the DMF will support, for example, original ANDA, ANDA amendment, or a PAS.

4. Statement certifying that the DMF is active and the GDUFA DMF user fee has been paid. DMF holders may submit a copy of Form FDA 3794 in the request submission to document payment of the GDUFA fee.

5. Statement that there is at least one valid Letter of Authorization (LOA) in the DMF intended to support the planned application submission.[20]

6. If the prior assessment request is to support an original ANDA submission, a citation to the Reference Listed Drug (i.e., the application number for the RLD), as provided in the Orange Book, and the drug product(s), including the strength(s), that will be included in the ANDA submission.

7. The planned submission date of the ANDA, ANDA amendment, or PAS. This date should be at least 6 months from the date the request is submitted to the DMF.[21]

8. (i). For an original ANDA, an ANDA amendment containing a response to a Complete Response Letter (CRL), or an amendment seeking approval of an ANDA that previously received a tentative approval, the applicable justification for the request from ***III.A items 1-5*** in this guidance[22] should be clearly stated in the cover letter.

   (ii). For a PAS to add a new API source, the applicable justification for the request from ***III.B items 1-2*** in this guidance[23] should be clearly stated in the cover letter.

Summary

- Pre- and Post-approval changes to drug substances
- Each drug substance manufacturer should assess the particular proposed modification(s) to determine the risk associated with the change(s)
- Close communication with NDA/ANDA applicant(s)
- Risk assessment – Impurity profile equivalence determination of intermediates and drug substances is a popular route taken to assess the risk associated with changes
- DMF prior assessment and eligibility

Resources

- FDA Guidance for Industry, Dec 2000: Alternate Source of the Active Pharmaceutical Ingredient in Pending ANDAs
  - www.fda.gov/regulatory-information/search-fda-guidance-documents/alternate-source-active-pharmaceutical-ingredient-pending-andas
- FDA Guidance for Industry, April 2004: Changes to an Approved NDA or ANDA
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/changes-approved-nda-or-anda
- FDA Draft Guidance for Industry, Sept 2018: Postapproval Changes to Drug Substances
  - www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM619947.pdf
- FDA Draft Guidance for Industry, Oct 2022: Review of Drug Master Files in Advance of Certain ANDA Submissions Under GDUFA
  - www.fda.gov/regulatory-information/search-fda-guidance-documents/review-drug-master-files-advance-certain-anda-submissions-under-gdufa
- ICH Q3A, Impurities in New Drug Substances (www.ich.org/page/quality-guidelines)
- ICH Q3C, Impurities: Guideline for Residual Solvents
- ICH Q3D, Guideline for Elemental Impurities
- ICH M7, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
- FDA Guidance for Industry, Sept 2020: Control of Nitrosamine Impurities in Human Drugs
  - www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs
- GDUFA-II Commitment Letter - www.fda.gov/industry/generic-drug-user-fee-amendments/submission-review
- GDUFA-III Commitment Letter - www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-iii-reauthorization