Change in API Supplier: Drug Product Quality Tips

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Learning Objectives

- Understand the **common reasons** for changing API source
- Identify required **CMC information** from the ANDA applicant
- Determine **ANDA supplement reporting category** for new API source
- Understand what **facility information** for API supplier is required in drug applications
- Understand the **impact of data integrity** violations on drug applications

Presentation Overview

- Drug product assessment perspective – **Rajib Paul, PhD**
  - **Common reasons** for alternate API source in pending ANDAs and ANDA supplements.
  - **CMC information** to support the new API source.
  - Post-approval **supplement reporting category** for new API source.
- Facility assessment perspective – **Bo Jiang, PhD**
  - OPMA **Facility Review** for API Supplier Change
  - OPMA **Data Integrity Assessment and Impact** on Applications

Drug Product Assessment Perspective

Common Reasons for Alternative API Source

- ANDA was approvable, except for an **unsatisfactory current good manufacturing practice (CGMP)** inspection for the primary API supplier.
- Application approval was delayed because **API supplier remained unacceptable/Inadequate**.
- Additional API supplier to **increase the capacity** of DP.
- **Withdraw** the original API supplier and add a new supplier.
- Alternate API source is applicable for pending **ANDAs and postapproval changes (ANDA supplements)**.

CMC Information for New API Source

- **Comparison** and justification of comparability (by the applicant) of the physicochemical properties and impurities of the API.
- **Drug substance manufacturer's certificates of analysis (COA) and drug product manufacturer's COA** for the drug substance from alternate API source.
- At least **one batch** of pilot or commercial scale **drug product (DP)** should be manufactured.
- Minimum of **3 months long-term and 3 months accelerated DP stability** data should be provided in the submission.

In-Vitro Testing of DP for New API

- **Comparative dissolution data** depending on the dosage form of the drug product should be provided.
- **DS high solubility** : Conduct comparative multipoint dissolution study using application/compendial medium & approved testing conditions.
- **DS low solubility** : Conduct comparative multipoint dissolution study using multi-pH media with approved testing conditions for DS pH dependent aqueous-solubility.
- Proposed change to new source of **DS is supported when comparative dissolution is similar**.

ANDA Supplement Reporting Category for Changing API Supplier

- Change from one drug substance manufacturer to another involves **more than simply a site change**.
- In most cases, there will be additional differences (e.g., **route of synthesis, process, solvents, equipment**).
- Alternate drug substance source should be reported in a **prior approval supplement (PAS)**.
- **Exception**: Approved API as a PAS in another ANDA from the same applicant; the applicant can **report the same alternate API source for their other drug products as a CBE-30**.

Case Study : CBE-30 Elevated to PAS

- Proposed Change: Alternate/New API source
  - Supplement submitted as CBE-30
- Decision: **Supplement denied to PAS by FDA**
- Reason: Alternate source of the API should be a PAS as per Guidance for Industry – Changes to an Approved NDA or ANDA Questions and Answers (January 2001), Manufacturing Sites – Q1/A1 and Draft Guidance for Industry – Post approval Changes to Drug Substances (September 2018), Section XI.
  - A change to a new source of the drug substance is considered to have **a high potential to have an adverse effect on the drug substance's impurity profile and physical properties**.

Case Study : Alternate API Source (…contd.)

- **Once the proposed alternate API source supplement is approved as a PAS for the same applicant**, and if there are no other changes to be reported that would otherwise belong in a PAS-type reporting category, **the applicant can report the same change (i.e., the same alternate API source) for their other drug products as a CBE-30**, provided the API manufacturing/testing site(s) has a satisfactory CGMP inspection status.

Resources

- Postapproval Changes to Drug Substances Guidance for Industry, DRAFT GUIDANCE, September 2018
- Guidance for Industry, Alternate Source of the Active Pharmaceutical Ingredient in Pending ANDAs, December 2000
- Changes to an Approved NDA or ANDA, Questions and Answers, January 2001
- Guidance for Industry Changes to an Approved NDA or ANDA, April 2004, Revision 1
- Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products, June 2013
- Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers, May 2014

Challenge Question

The applicant should provide certificates of analysis (COA) for the alternate drug substance from:

A. Drug substance manufacturer

B. Drug product manufacturer

C. Both drug substance and drug product manufacturers

Facility Assessment Perspective

API Supplier Facility Information

- Applies to all API supplier related facility
- Accuracy of information on facilities
  - Clear roles & responsibilities
    - Development, exhibit batches, and commercial operations
    - Manufacturing (intermediate and final DS), testing (routine or characterization), storage
    - Consistent between DMF, 356h, and 3.2.S
  - Include all intermediate sites
  - Complete facility list - all facilities support the subject application, revised LOA needed if a subset of facilities are proposed

API Supplier - OPMA Facility Assessment

- Risk-based approach
  - Roles & responsibilities
  - Facility experience & inspection history available
    - Chemical synthesis, fermentation, extraction, purification, testing,
- Pre-approval inspection
  - Impact on application timeline
- Facility CGMP compliance status
  - Can change before application goal date due to CGMP violations
  - Non-compliant OAI status prevents application approval

API Supplier Change – Facilities

- Pre-approval
  - Additional API supplier - complete & accurate facility information
  - Withdraw the original supplier and add new supplier
    - Any confirmed DI issues with the original supplier may impact data reliability in submission
- Post-approval
  - Withdraw the original supplier and add new supplier
    - Any confirmed DI issues may warrant further assessment of the original data based which application was approved

Data Integrity Assessment Overview

- Importance of Data Integrity (DI)
  - FDA must have confidence that data in the application is a true and reliable representation of drug product quality, breach in DI erodes/breaks trust
  - Mostly discovered during inspections – tip of the iceberg, when confirmed, all data in submission are in question
- FDA Assessment of DI violations
  - Lengthy and resource-intensive process, assessments by ORA, OMQ/OC, OPMA/OPQ, and other offices
  - CGMP Violations (testing into compliance, data delete/falsification, OOS not investigated, IAQ controls on data, etc.)
  - Scope (pattern, practice, time period, GMP systems, facility involved)
  - Impact on pending and approved applications

DI Assessment on Original API Supplier

- Collaborative effort with ORA and OMQ
  - Parallel assessment performed along with OMQ
  - Assess data validity - 3rd party forensic analysis and DI audit report
  - Assess materiality of application data (e.g., biobatch/ exhibit/ registration batches)
- Assessment outcome - Application specific
  - No DI concerns / indeterminate DI (may send RAI or follow-up inspection) / confirmed data unreliability (CRL)
  - Request 3rd party independent testing, request new batches (DS and DP) and conduct new BE study
  - Delay in application approval - Facility OAI status prevents approval - All applications using the subject API supplier/DMF

Case study – DS Facility Background

- DS facility compliance history
  - Sep 2000 inspection, 483 citation, inadequate control on analytical data and e-data, OAI to VAI,
  - July 2002 inspection, OAI, 483 observations: analytical data DI persist - unauthorized data access, routine sample retesting w/o justification, data deletion;
  - Warning letter issued: inadequate control to prevent unauthorized access or change to data (retesting, deletion, back-dating, re-integration to obtain passing results; Failure to adequately investigation deviations; failure to follow lab controls at the time of performance)
  - Regulatory meeting and T-con with expectation provided to the firm
- Parallel to OMQ assessment, OPQ has identified the time period (since Sept 2000) that data are impacted by the DI violations

Case study – Application Impact

- DS lot used in manufacturing of the DP bio-batch was manufactured in Feb2003, therefore, DS data are considered unreliable and impacting BE study outcome, CRL was sent and requested
  - Option 1, Provide additional info to confirm the quality of the original DS lots (3rd party DI assessment on all the data of the DS lots used in the DP bio-batch, any OOS, investigations, and any corrective actions), or
  - Option 2, manufacture new DP batch with new DS lot from the original DS site (only after implementing sufficient corrective actions to the facility that have been verified by the FDA to support the reliability of newly submitted data), and new pivotal BE data, or
  - Option 3, manufacture new DP batch with DS lot from a new CGMP compliant DS source, and new pivotal BE data
- Response to CRL - Original DS site withdrawn (DMF holder confirmation/certification letter provided (no DI observations in the 3rd forensic assessment, manufactured under GMP and inline with DMF), no DI audit report
  - Include a new DS source with new DP batch data, no new BE study
- Proposal not acceptable. Information Request (IR) sent – request again data in Option 1 above
- Response to IR – commit to Option 3 above, and the application was CR - BE review inadequate

Additional Resources

- Guidance for industry, Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Q&A. Oct 2019.
- Draft Guidance for Industry, FDA Data Integrity and Compliance with CGMP. Apr 2016
- Guidance for Industry, FDA Data Integrity and Compliance with Drug CGMP, Q&A. Dec 2018
- PIC/S Guidance - Good Practices for Data Management and integrity in Regulated GMP/GDP Environments. Jul 2021
- MHRA Guidance - 'GXP' Data Integrity Guidance and Definitions. Mar 2018
- WHO Guidance on Good Data and Record Management Practices. 2016
- Guidance for Industry, Part 11, Electronic Records; Electronic Signatures - Scope and Application. Aug 2003
- EU Annex 11, Computerized Systems. Jan 2011

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Challenge Question #1

What facility information for API supplier is required in drug applications?

A. Clear and consistent roles & responsibilities between the DMF and the application

B. Complete manufacturing, testing, and storage facilities for all intermediates and final drug substance

C. LOA should specify facilities for commercial operations if a subset of facilities are proposed

D. All of the above

Challenge Question #2

When data integrity issues are confirmed at a API manufacturing facility, which of the following can happen to drug applications?

A. Request independent testing and additional info to assure DS data quality

B. Manufacture new batches using alternative API supplier and conduct new BE study

C. Facility OAI status prevents approval of all applications using the subject API supplier

D. All of the above