Division of Filing Review: Helpful Tips for Submission of ANDAs and Controlled Correspondences

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Generic Drugs Forum 2021: Lifecycle of a Generic Drug - April 28, 2021

Discussion Overview

- Tips:
  - Common Major (RTR) Deficiencies
  - Common Minor Deficiencies
  - Controlled Correspondence
- Resources

Refuse-to-Receive (RTR) Statistics

	FY 2018 (Oct. 2017- Sept. 2018)	FY 2019 (Oct. 2018- Sept. 2019)	FY 2020 (Oct. 2019- Sept. 2020)
Total ANDAs Submitted	1057	923	865
ANDAs Refused	88 (8.33%)	47 (5.09%)	40 (4.62%)

Common Major Deficiencies (FY 2020)

- Stability related issues
- Not Q1/Q2 same to reference listed drug (RLD)
- Inadequate dissolution
- Inadequate Justification of Impurities
- Incomplete/Failed bioequivalence (BE) studies
- Inadequate justification of excipients

Major Deficiency-related Filing Tips

Stability Data

- Provide a minimum of three test batches manufactured using at least two active pharmaceutical ingredient (API) lots of each strength
- Accelerated and Long Term stability studies
  - Include 6 months' (180 days) worth of data with three time points
  - Intermediate studies for all three batches of the specific strength if accelerated stability study shows significant change or failure of any attribute
  - Orientation of stability studies
    - Provide both worst case and non-worst case orientation for liquids, solutions, semi-solids, and suspensions
  - Provide all stability start and pull dates and ensure they are accurate

Q1/Q2 Sameness

- 21 CFR 314.94 (a)(9)(iii-iv)
  - Applicant must provide justification for any changes to exception excipients
  - Before submitting an ANDA, applicants may submit a controlled correspondence to request a Q1/Q2 evaluation of their proposed drug product

Dissolution

- Follow Product-Specific Guidance (PSG) recommended dissolution studies
- Half-tablet dissolution should be provided for modified-release products, where applicable
- Minimum of 12 dosage-units comparative dissolution for each strength of test product and RLD

Justification of Impurities

- Specified identified impurity or degradation product
  - Proposed acceptance criteria (AC) should not exceed regulatory qualification threshold (QT)
- Specified unidentified impurities or degradation product
  - Proposed AC should not exceed Identification Threshold (IT)
- *Supportive data and information (justification) should be provided if AC exceeds QT or IT*
- Unspecified Impurities
  - Proposed AC should not exceed IT
  - Cannot cite USP as a justification
- Reference is made to Guidance for Industry ANDAs: Impurities in Drug Substance and Guidance for Industry ANDAs: Impurities in Drug Products

BE Studies/IID Justification

- BE Study Data
  - Provide data for passing BE studies in Module 2.7

- Inactive Ingredient Database (IID) justification of excipients
  - IID justification for oral liquids should be per dosage unit based on RLD dosing information in the labeling
  - Justify all flavoring agent components. Provide any Drug Master File (DMF) letters of authorization, if needed, along with all applicable information or composition breakdown

Minor Deficiency-related Filing Tips

Module 1

- Form FDA 356h
  - Consistent patent certification between field 20 and module 1.3.5.2
  - Chemical name in field 11
  - List all proposed strengths in field 6 (including fill volumes)
  - DMF numbers listed in field 29 and module 1.4.2
- Environmental Impact Analysis Statement or claim of categorical exclusion must be provided by the applicant

Module 1 (continued)

- Basis of Submission
  - Provide the appropriate Basis of Submission
    - Designate RLD and Reference Standard (RS) (if applicable) currently listed in the Orange Book (refer to the Guidance for Industry: Referencing Approved Drug Products in ANDA Submissions {October 2020}).
  - Proposed strength approved via Suitability Petition (SP)
    - SP Docket number **and** FDA's correspondence approving the petition

- Module 1.12.12, provide side-by-side (SBS) labeling comparison against the RLD

Module 1 (continued)/Module 2

- Module 1.14
  - Legibility of draft and RLD container labels
  - Provide the proposed container and carton labels for each strength and each packaging configuration (container size) (Module 1.14.1.1)
  - Provide the RLD container and carton label for each strength (Module 1.14.3.3)
  - Comparison may be made to the RS only if RLD labeling is not available, but all efforts should be made to locate RLD labeling information, and this should be clearly stated

- Module 2
  - Provide separate PDF and Word documents

Module 3

- Module 3.2.P.1 (Composition table):
  - Provide proposed formulation in terms of %w/w, %v/v, and %w/v, as applicable
  - Provide mg/dose for oral suspensions and oral solutions
  - Provide grade, purity, hydration state* for excipients, as applicable (*add footnote for water correction)

Module 3 (continued)/Module 5

- Modules 3.2.S.4.5 and 3.2.P.5.6
  - Justification of Specifications Tables
    - Follow recommended format for tables
    - Provide separate tables for Specified Identified, Specified Unidentified and Unspecified Impurities
- Module 5:
  - Provide adequate Study Tagging files

Considerations for Entire ANDA

- English translation for ALL documents
- eCTD deficiencies:
  - Follow eCTD and PDF specifications
  - Descriptive leaf titles
  - Adequate and descriptive bookmarks and/or hyperlinks
  - Documents must be placed in correct location
  - Check for completeness of all folders, subsections, and leaflets
  - Ensure there are no duplicate files by using the correct modifying operator
  - Contact CDER ESUB at esub@fda.hhs.gov

Controlled Correspondence: Division of Filing Review

- Types of Controlled Correspondence inquiries
- Controlled Correspondence Tips
- Controlled Correspondence review disciplines

Types of Controlled Correspondence Inquiries Received in DFR

- Standard Controlled Correspondence
  - Q1/Q2 evaluation
  - Inactive ingredients evaluation
  - Filing strategies

Controlled Correspondence Tips

- Include the diluent formulation for co-packaged products for Q1/Q2 assessments
- Indicate total fill volumes (total drug content) for parenteral products
- Specify any water correction for inactive ingredients for which multiple hydration states are applicable
- Include all applicable units for all inactive ingredients

Controlled Correspondence Review Disciplines

- OGD's Office of Bioequivalence
- OGD's Office of Research and Standards
- OGD's Office of Regulatory Operations, Division of Filing Review
- OGD's Office of Regulatory Operations, Division of Labeling Review
- OGD's Office of Generic Drug Policy
- OPQ's Office of Policy for Pharmaceutical Quality

Challenge Question #1

Which of the following does not review Controlled Correspondences?

a. Division of Quality Management Systems
b. Division of Filing Review
c. Division of Labeling Review
d. Office of Bioequivalence

Challenge Question #2

Which group reviews the ANDA to determine whether it is substantially complete?

a. Division of Quality Management Systems
b. Division of Filing Review
c. Division of Labeling Review
d. Office of Bioequivalence

Additional Resources

- MAPP 5200.14 Filing Review of Abbreviated New Drug Applications
- Guidance for Industry ANDA Submissions — Content and Format of Abbreviated New Drug Applications (Revision 1, June 2019)
- Guidance for Industry ANDA Submissions – Refuse-to-Receive Standards (Revision 2, Dec. 2016)
- Guidance for Industry ANDA Submissions – Refuse to Receive for Lack of Justification of Impurity Limits (Aug. 2016)
- Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products Questions and Answers (May 2014)
- Guidance for Industry: Referencing Approved Drug Products in ANDA Submissions (October 2020)
- Guidance for Industry Controlled Correspondence Related to Generic Drug Development (November 2020)
- GDUFA II Commitment Letter
  https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm

Contact

- Controlled Correspondence:
  - genericdrugs@fda.hhs.gov
- ANDA Filing Status:
  - ANDAFiling@fda.hhs.gov
- DFR Rescission Requests or RTR questions:
  - DFRSupervisor@fda.hhs.gov


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