Division of Filing Review: Best Practices for ANDAs and Controlled Correspondence Submissions

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Learning Objectives

- Refuse-to-Receive (RTR) Statistics
- Common Major (RTR) Deficiencies
- Common Minor Deficiencies
- ANDA Submission Considerations
- Communication with DFR PM
- Controlled Correspondence
- References/Contact

Refuse-to-Receive (RTR) Statistics

	FY 2018 (Oct. 2017 – Sept. 2018)	FY 2019 (Oct. 2018 – Sept. 2019)	FY 2020 (Oct. 2019 – Sept. 2020)	FY 2021 (Oct. 2020 – Sept. 2021)
Total ANDAs Submitted	1057	923	865	**808**
ANDAs Refused (RTR)	88 (8.33%)	47 (5.2%)	40 (4.62%)	**38 (4.70%)**

Common **Major** Deficiencies (FY 2021)

- Stability Data
- Qualitatively/Quantitatively (Q1/Q2) Same as the Reference Listed Drug (RLD)
- Dissolution Studies
- Justification of Impurities
- Bioequivalence Studies
- Inactive Ingredient Justification

Stability Data

- Minimum of **three** test batches manufactured using at least **two** active pharmaceutical ingredient (API) lots of each strength
- **Six months (180 days)** worth of accelerated and long-term study data with **three** time points
- Conduct **intermediate studies** if accelerated stability study shows significant change or failure of any attribute
  - **Accelerated studies should still be continued to 6 months even if failure is detected**

Stability Data (Continued)

- Orientation of stability studies for both worst-case and non-worst-case scenarios
- Stability start and pull dates should be submitted for all batches and timepoints

Q1/Q2 Same to the RLD

- **Parenteral** drug products must contain the same inactive ingredients and in the same concentration as the RLD pursuant to 21 CFR 314.94 (a)(9)(iii)
- Exception excipients are permitted
  - Preservatives
  - Buffers
  - Antioxidants

Q1/Q2 Same to the RLD (Continued)

- **Ophthalmic or Otic** drug products must contain the same inactive ingredients and in the same concentration as the RLD pursuant 21 CFR 314.94 (a)(9)(iv)
- Exception excipients that can differ from the RLD (except for Ophthalmic drug products)
  - Preservative
  - Buffer
  - Substance to adjust tonicity
  - Thickening agent

Q1/Q2 Same to the RLD (Continued)

- In **ophthalmic** drug products, applicant may not change the following:
  - A buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the RLD
- Deviation in Q1/Q2 with respect to exception excipients should be accompanied with an appropriate in vivo BE study(ies)
- Refer to 21 CFR 314.94 (a)(9)(iv) for more details

Dissolution Studies

- Product-Specific Guidance (PSG) **recommended** dissolution studies
  - Refer to Dissolution Methods database for completeness
- **Half-tablet dissolution studies** for functionally scored or modified-release products, where applicable
- Comparative dissolution studies should include a minimum of **12 dosage-units** for each strength of test product and RLD

Justification of Impurities

- For specified **identified** impurity or degradation product, Acceptance Criteria (AC) should not exceed Regulatory Qualification Threshold (QT)
- For specified **unidentified** impurities or degradation product, 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
  - Should not cite USP exclusively as a justification (Refer to Impurities RTR Guidance)

Bioequivalence Studies

- Bioequivalence (BE) Study Data should be provided in recommended tabular format
- Follow Model BE Data Summary Tables as outlined in DFR checklist
- Long-Term Storage Stability (LTSS) should exceed Sample Storage duration
- Information in LTSS tables, Table 10, and Table 4 should be consistent with information provided in the Module 5 reports

Inactive Ingredient Justification

- Inactive ingredient justification for oral liquids should be **per dosage** unit based on RLD dosing information in the labeling
- Justification should be performed against the same route of administration
- Justify all flavoring agent components, colorants, and fragrances.
- Provide any Drug Master File (DMF) letters of authorization, if needed, along with all applicable information or composition breakdown

Common **Minor** Deficiencies (FY 2021)

- Module 1
- Module 2
- Module 3
- Module 5
- Entire ANDA Submission

Module 1

- Form FDA 356h
  - Inconsistent patent certification between field 20 and module 1.3.5.2
  - Provide information of the U.S. Agent in field 6 (if applicable)
  - List all proposed strengths in field 13 (including fill volumes)
  - DMF #s listed in field 29 and module 1.4.2
- Environmental Impact Analysis Statement or claim of categorical exclusion must be provided by the applicant in Module 1.12.14 (21 CFR 314.101(d)(4))

Module 1 (continued)

- In Module 1.3.5, address all patents currently listed in the Orange Book
- Basis of Submission *(Referencing Approved Drug Products in ANDA Submissions Guidance for Industry, October 2020)*
  - Designate the appropriate RLD currently listed in the Orange Book
  - Proposed change approved via Suitability Petition (SP)
    - SP Docket number and FDA's correspondence approving the petition

Module 1 (continued)

- Module 1.14
  - Provide the proposed container and carton labels for each strength and each packaging configuration (container size) (Module 1.14.1.1)
  - Provide the package insert in SPL format or provide a commitment to provide the proposed labeling in SPL format (Module 1.14.2.2)
  - 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 for Modules 2.3 and 2.7
- Provide Table 5 (Summary of In-Vitro Dissolution Studies) for all submitted comparative (test and reference) dissolution studies for all strengths
- Provide exact location of LTSS study reports and data

Module 3

- Module 3.2.P.1 (Composition table):
  - Provide proposed formulation in all units including %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)

- 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 3.2.S.4.3
  - Provide spectra and chromatograms for reference standards and test samples for the drug substance

Module 3 (continued)

- Module 3.2.P.8
  - Provide withdrawal dates for each time point for all stability studies

Module 5

- List all (pilot and/or pivotal) studies in Module 5.2
- Provide adequate Study Tagging files
- In Module 5.3.1.4 provide 20% chromatograms for all analytes of all accepted runs from the fasting and fed study

ANDA Submission Considerations

- English translation for ALL documents
- eCTD deficiencies:
  - Pages that are not easily legible
  - Pages that are not oriented correctly
  - Submissions without adequate and descriptive bookmarks and/or hyperlinks
  - Documents not placed in the correct location

- Tips
  - 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 for any questions

Communication with DFR PM

- **DFR PM will place courtesy call to <u>notify of imminent communication</u>**
- A secure email and fax number for the U.S. Agent (Box 6 of 356h) or Responsible Official (Box 33 of 356h) should be provided
- Alternative contact person can be listed if out of office

Controlled Correspondence Learning Objectives

- Types of controlled correspondence reviewed by DFR
- Helpful information for submitting each type of controlled correspondence

Types of controlled correspondence reviewed by DFR

- Q1/Q2 formulation assessment
- Inactive ingredient justification per unit dose
- Filing Strategies

Requests for Q1/Q2 Formulation Assessment

- Q1/Q2 the same as the RLD
  - 314.94 (a)(9)(iii-iv)
- Submit no more than three formulations in a single controlled correspondence
- Submit separate Q1/Q2 formulation assessment for drug product with multiple strengths
  - Each strength is a sperate drug product
- Ensure the proposed formulation table is clear and unambiguous as possible
  - Salt and hydration form, purity, grade, type, and function of ingredients.
- FDA will not review proposed formulations that are not required or FDA-recommended in guidance to be Q1/Q2 to the RLD

Requests for Q1/Q2 Formulation Assessment (Continued)

- Indicate total fill volumes (total drug content) for parenteral products
- Include the diluent information for co-packaged products for Q1/Q2 assessments
- Include all applicable units for all inactive ingredients

Requests Related to Inactive Ingredients

- Request no more than three inactive ingredient assessment in any given controlled correspondence
  - Three inactive ingredients with one proposed level of use each, OR
  - One inactive ingredient with three proposed levels of use
- Identify the RLD

Requests for Filing Strategies

- Submit a particular element of generic drug development
  - Example: acceptability of submitting multiple strengths of a drug product in a single ANDA.

Q&A

- Which of the following is a common eCTD deficiency? Choose all that apply.
  - (A) Pages that are not easily legible
  - (B) Pages that are not oriented correctly
  - (C) Submissions without adequate and descriptive bookmarks and/or hyperlinks
  - (D) Documents that are not placed in the correct location

- Which information does **not** need to be included in the controlled correspondence?
  - (A) fill-volume
  - (B) Route of administration
  - (C) market status of the RLD
  - (D) Estimated ANDA submission time-frame

References

- 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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