Proactive Strategies to Avoid Major Filing Deficiencies & Other Stumbling Blocks

Truong-Vinh (Vinh) Phung, PharmD
Commander, US Public Health Service
Regulatory Officer
Division of Filing Review (DFR), Office of Generic Drugs (OGD)
CDER | US FDA
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Learning Objectives

- Understand OGD's Mission and DFR's Purpose
- Leverage FDA resources
- Recognize filing major deficiencies
- Describe stumbling blocks
- Provide justifications to deviate from requirements and/or recommendations

Mission

- Ensures high-quality, affordable generic drugs are available to the American public
- Filing review determines whether an ANDA is substantially complete to permit substantive review
- Division of Filing Review's objective:
  - File substantially complete ANDAs (ideally, without issuing an Information Request)
  - Maintain and apply uniform review standards

FDA Resources

- ANDA Submissions – Refuse-to-Receive Standards (December 2016)
- ANDA Submissions – Refuse-to-Receive Standards: Questions and Answers (October 2017)
- ANDA Submissions – Refuse to Receive for Lack of Justification of Impurity Limits (August 2016)
- ANDA Submissions – Content and Format of ANDAs (June 2019)
- Filing Review of ANDAs MAPP 5200.14 (includes filing checklist)

FDA Resources

- ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers (May 2014)
- Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products (June 2013)
- Content and Format of Composition Statement and Corresponding Statement of Ingredients in Labeling in NDAs and ANDAs (April 2024)
- Communicating Certain Deficiencies Identified during Filing Review of ANDAs MAPP 5220.3
- Product-Specific Guidances (PSG)

Key

- Major
  - A deficiency that would result in a refuse-to-receive (RTR)
- Stumbling Blocks
  - Impacts the ability to file an ANDA
- Information Request
  - Certain circumstances in which the filing team needs further information, clarification, action, or confirmation that data/info is in the original ANDA submission

Module 1

- Majors
  - Form FDA 356h
  - No legal Basis of Submission (BOS)
- Stumbling Blocks
  - Lack of appropriate signatures on 356h
  - Approved Suitability Petition (SP): docket number and copy of FDA's approval letter
- Information Request
  - Minor deficiency to administratively correct the BOS, provide SP information, or withdraw if an NDA is approved for the same change as the approved SP

Module 2: in vitro data

- Majors
  - Missing comparative (Test vs RLD) dissolution data/media
  - Missing Comparative Physiochemical Data of Ophthalmic Solutions
- Stumbling Blocks
  - Comparative data for each strength (Table 5 BE table and 12-unit) placed in another eCTD section or not in the original submission
  - Comparative data for ophthalmic solution (Table 17 BE table)
- Information Request
  - Minor deficiency will ask to point out the location of the data in the original submission (and provide BE summary)

Module 2: in vivo data

- Majors
  - Not following PSG recommendations and justification not provided
  - Only providing failed bioequivalence (BE) study or studies
  - Missing Long-Term Storage Stability (LTSS) data or LTSS < sample storage days
- Stumbling Blocks
  - Publication of new/revised PSG and timing of ANDA submission
  - Cross-referencing BE studies
- No Information Request
  - These are not considered a minor deficiency

Module 3.2.S

- Major
  - Type II active pharmaceutical ingredient DMF and an Incomplete Completeness Assessment (CA)
- Stumbling Blocks
  - Type II DMF is not on the public available for reference list
- Information Request
  - This is not considered a minor deficiency

Justification of Specifications

- Major (Modules 3.2.S.4.5 and 3.2.P.5.6)
  - Proposing limits that exceed qualification thresholds (QT) and/or identification thresholds (IT) without a justification
- Stumbling Block
  - Unspecified Impurities exceed QT and/or IT even in cases with USP monographs
- Information Request
  - This is not considered a minor deficiency unless tables are not in recommended format or a discrepancy that warrants clarification

Module 3.2.P.1

- Majors
  - Use of an inactive ingredient at a level that exceeds any of the inactive ingredient database (IID) listings without a justification
  - Non-Q1 and/or non-Q2 formulation
- Stumbling Blocks
  - Ophthalmic drugs: Q1/Q2 deviations, per 314.94(a)(9)(iv), from the RLD should be accompanied by an in vivo BE study or studies
  - Differences in pH adjusters and waiver requests
  - Q1/Q2 sameness requirements and recommendations in PSGs
- Information Request
  - These are not considered a minor deficiency

Module 3.2.P.3.3

- Major
  - Missing master production (blank manufacturing) records
- Stumbling Block
  - Common blend used in exhibit batches but not intended for commercial production
- Information Request
  - This is generally not considered a minor deficiency

Module 3.2.P.3.5

- Major
  - Missing validation (bacterial retention) study of sterilizing 0.2-micron grade filter(s) for aseptically filled products
- Stumbling Block
  - Study/data buried within other reports or placed in an incorrect eCTD section
- Information Request
  - Minor deficiency will ask to point out the location of the study report in the original submission

Module 3.2.P.8

- Majors
  - Not using 2 API lots for each strength
  - Missing stability data, <three time points, <180 days (i.e., 6 months)
  - Missing worst-case and non-worst-case orientations
- Stumbling Blocks
  - Unclear/typographical errors
  - Missing stability initiation dates and/or pull dates
  - Duplicate stability data
- Information Request
  - These are not generally considered a minor deficiency unless information or clarification is needed

Module 3.2.R

- Majors
  - Missing executed production records for all manufactured batches
  - Solid oral dosage forms: <100,000 units packaged in marketed container closure system (CCS) for each strength
- Stumbling Blocks
  - Duplicate executed production records
  - Clear intentions of marketing CCS without supporting stability data, missing CCS information in module 3.2.P.7, and/or labeling in module 1.14.1
- Information Request
  - These are not generally not considered a minor deficiency

Minor Deficiencies

- Major
  - 10 or more minor deficiencies
- Stumbling Blocks
  - Issues with technical eCTD submission
  - Not following the Filing MAPP/Checklist
- Information Request
  - Not applicable unless there are 9 minor deficiencies or less

Justifications

- Provide to deviate from recommendations (e.g., alternative approach)
- Demonstrate that it satisfies the requirements of the applicable statutes and regulations
- Submit in the cover letter or in the specific module/section to draw the reviewer's attention
  - Needs to be provided in the ANDA as originally submitted to be considered substantially complete

Key Takeaways

- Applicants can submit a justification to use an alternative approach to avoid an RTR if it satisfies the requirements of the applicable statutes/regulations
- Be proactive and provide justifications upfront (either in the cover letter or the specific module/section)
- If an Information Request is sent, pay attention to each deficiency, adequately address each, and submit a response within the prescribed timeframe
- Remember: DFR's objective is to file substantially complete ANDAs to permit a substantive review