An Overview of the Draft Guidance ANDA Submissions—Refuse-to-Receive Standards
Statistics
497 ANDAs Refused-for-Receipt between CYs 2009-2012:

- 12% (2009)
- 18% (2010)
- 15.5% (2011)
- 9.4% (2012)
For 2012, 100 ANDAs were Refused-for-Receipt:

- 40 (serious bioequivalence deficiencies)
- 36 (serious chemistry deficiencies)
- 13 (organization/formatting deficiencies)
- 6 (clinical deficiencies)
- 4 (inadequate sterility assurance)
- 1 (incorrect basis of submission)
Draft RTR guidance was mandated by GDUFA:

“FDA will develop enhanced refusal to receive standards for ANDAs and other related submissions by the end of year 1 of the program and will publish such standards in advance of implementation.”

- Generic Drug User Fee Act Program Performance Goals and Procedures

Draft guidance was published on Sept. 30, 2013 (FDA/2013-D-1120)
Current Policy
In General, eCTD, and Expedited Review
An ANDA containing less than 10 easily remedied deficiencies will be contacted regarding the same. A response must be provided within 10 U.S. business days.

An ANDA will be Refused-for-Receipt if:

- The number of easily remedied deficiencies is equal to or more than 10

- A response to the fewer than 10 deficiencies is not received within 10 U.S. business days
An ANDA should be formatted according to eCTD format (*submissions must be in electronic format to be eligible for GDUFA metrics)

-ANDAs submitted as a single, continuous, unbookmarked PDF file will be Refused for Receipt

-Use place holder (title pages) for sections not applicable to your application. In other words, do not omit files!

-Provide a technical POC along with the designated contact agent/personnel

If submitting through the Electronic Gateway, **it is incumbent upon the applicant to confirm that the submission was received and processed without issue.** No consideration will be given to restoring an original submission date in the event the processing of an ANDA submission is delayed due to corrupted files.
The following guidances are useful resources for recommendations pertaining to electronic submissions:

- Guidance for Industry *Providing Regulatory Submissions in Electronic Format*—ANDAs


- Guidance for Industry *Providing Regulatory Submissions in Electronic Format*—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications
Expedited Review Requests

On the Cover Letter, indicate in boldface “Expedited Review Requested” or “Eligible for Expedited Review, GDUFA Year 1 or 2 Cohort”
Module 1: Administrative

- Form FDA 356h
  - If the applicant is a foreign entity, fill out the U.S. agent information in Field 6 and be sure the U.S. agent countersigns the form (21 CFR 314.50(a)(5)) *(If no U.S. agent-Refuse to receive)*
  - Field 15 (Orphan Drug Designation): Only pertains to the applicant **holding** the ODE
  - If a signed scanned copy is submitted, be sure to also submit a fillable pdf (unsigned) copy of the 356h
Module 1: Administrative (cont.)

- A suitability petition may be relied upon as a basis of submission only after it has been approved (21 CFR 314.94(a)(3)(i)). Be sure to include a copy of the approved suitability petition in the ANDA submission (21 CFR 314.94(a)(3)(iii))

- Form FDA 3674 (originals, new strength amendments and prior approval supplements)

- Select A, B, or C based on whether the particular submission relies on clinical data
Module 2: Summaries

- QOS (2.3.S and 2.3.P)
  - Submit these in both MS Word and pdf

- Clinical Summary (Bioequivalence) (2.7)
  - Revised tables 3, 10, and 16, and new table 17
  - New tables for *In Vitro* Binding Bioequivalence Study Summary and SAS Transport Formatted Tables for Dataset Submission
  - Table 5 (dissolution summary) should be included for all media/studies and for all strengths
Module 2: Summaries

- Clinical Summary (Bioequivalence) (2.7)(cont.)
  
  • If Table 10 is missing, or the information in the last two rows is not provided or does not adhere to the recommendations below, the ANDA will be **Refused for Receipt**
  
  ➢ LTSS Coverage should be equal to or more than the no. of days for sample storage duration
  
  ➢ The temp. reported for LTSS Coverage should be within or less than the temp. range for sample storage

• If Table 17 is missing for an ophthalmic solution, the ANDA will be **Refused for Receipt**, despite a Q/Q same test formulation
Module 3: Drug Substance (3.2.S)

- (a)(3)(F) applications
  - These are applications identified under GDUFA that do not rely on a Type II API DMF reference
  - The information provided in this section will be subject to a review process similar to the Completeness Assessment (for Type II API DMFs)
  - Any deficiencies revealed in the API review will be communicated to the applicant by the filing reviewer. If a response is not received within 10 U.S. business days, the ANDA will be **Refused for Receipt**
Module 3: Drug Substance (3.2.S)  
– (a)(3)(F) applications (cont.)

FDA will Refuse to Receive an ANDA if either of the two deficiencies is revealed either in an (a)(3)(F) review or an Initial Completeness Assessment:

– Improperly designated starting material for the API

– Missing sterility assurance data for a sterile API
Module 3: Drug Product (3.2.P)

– Justifying oral liquids
  • Do not rely on percentages that are listed in the IID for justification of a level of use for an inactive

– Q/Q sameness evaluations
  • With these types of justifications, also justify the proposed concentration/amount via the IID
  • Provide evidence that any changes permitted by 21 CFR 314.94(a)(9)(iii)(iv) do not affect safety and/or efficacy of the drug product

– Flavoring agents
  • Provide qualitative and quantitative breakdown of components
Module 3: Drug Product (cont.)

- For any inactive ingredient that cannot be justified via the IID, submit or provide any of the following:
  
  • Pharm/tox information
  
  • Evidence of a CDER-approved drug product of the same route of administration as the test product that contains the inactive ingredient in question at or above the proposed level of use
  
  • A Controlled Correspondence requesting an evaluation of the acceptability of the proposed level of use

(http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm120610.htm)

If the proposed level of use cannot be justified via the IID and none of the above support is provided at the time of submission, the ANDA will be Refused for Receipt.
Module 3: Drug Product (cont.)

- Elemental Iron: Per 21 CFR 73.1200(c), the amount of elemental iron ingested per day may not exceed 5 mg. Provide calculations!

3.2.P.3.3 (Manufacturing)
- Blank and executed batch and packaging records are to have clear, legible English language translations if not a separate document (Refuse to Receive)
  - Font size for English language text should be the same as for the foreign language text
  - Any handwritten notes are to be translated as well
  - See 21 CFR 314.101(d)(5)
Module 3: Drug Product (cont.)

3.2.P.7 (Container/Closure)

- Information/data for all proposed container/closure systems proposed for marketing should be included in this module
  - Test/specifications (blank certificates of analysis)
  - Executed certificates of analysis
  - Technical drawings/diagrams

- Include data from water permeation and light transmission studies
- Include leachable/extractable study data for liquid drug products in plastic containers
Module 3: Drug Product (cont.)

3.2.P.8 (Stability)

The following points are reflective of current recommendations.

- Only **one** batch required
- 3 months’ worth (= 84 days) of accelerated data
- Initiation date(s) and pull dates (84-day minimum based on these!)
- Container orientation (for liquid and semi-solid dosage forms)
- Proposed expiration date for bulk packaging
Module 3: Drug Product (cont.)
3.2.P.8 (Stability)
Inadequate Stability (current) (Refuse to Receive)

- Accelerated stability data covering a period <84 days
- No inverted (or horizontal) accelerated data for liquid and semi-solid dosage forms
Module 3: Regional

Current Packaging Considerations

– Solid Oral Dosage Forms (100,000 dosage units)
  • Container labeling
  • Container/closure information in 3.2.P.7
  • Accelerated stability data for all packaged configurations, including bulk if counted toward the 100K minimum
  • Executed packaging records

– Transdermals
  • Three distinct lots of laminate must be utilized to produce 25,000 units per strength
Special Refuse-to-Receive Considerations (Be the same as the RLD!)

- Scoring

- Injectable fill Volumes

- Special Packaging (e.g. blister packaging)

- Conditions of Use
  - Exception: Indication/MOU or unexpired exclusivity carve-outs
  - Exception: Labeling differences allowed pursuant to an approved suitability petition
Module 5: Clinical Study Reports

• Failed Studies must be submitted (See the Requirements for Submission of Bioequivalence Data; Final Rule, 74 FR 2849, 2862 (Jan. 16, 2009); the guidance for industry Submission of Summary Bioequivalence Data for ANDAs; and 21 CFR 314.94(a)(7)(i))

• An ANDA will be Refused for Receipt if only a failed study is submitted

  – SAS files
    • Needed for all BE studies performed
    • Individual subject concentrations should comprise columns rather than rows
Module 5: Clinical Study Reports (cont.)

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Module 5: Clinical Study Reports (cont.)

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Module 5: Clinical Study Reports (cont.)

– *In-Vitro* Dissolution
  • Provide the RLD certificate of analysis for all strengths (place these in Module 2.7 as well)
  • Check specific bioequivalence drug product guidances for dissolution recommendations

**Dissolution Recommendations (If incomplete or absent, Refuse to Receive)**
  • 12 unit vs 12 unit for **all strengths** in **all** recommended media
  • 12 half-tablet units for any dosage form for which this information is necessary*
  • Don’t forget about alcohol dose-dumping studies, if applicable!
Planned Implementation Date of “new” items:

Upon issuance of the final guidance.
An ANDA containing less than 10 easily remedied deficiencies will be contacted regarding the same. A response must be provided within 5 U.S. business days. Day 1 of the 5 U.S. business days will commence the day after notification is provided to the applicant.

An ANDA will be **Refused-for-Receipt** if:

- The number of easily remedied deficiencies is equal to or more than 10

- A response to the fewer than 10 deficiencies is not received within 5 U.S. business days
Module 1: Administrative

– Form FDA 356h

• Include all facility information in Field 29 and use continuation pages as needed (do not use attachment sheets!)

• Facility info should still be included in 3.2.S.2 and 3.2.P.3.1, respectively

• Include all contact information and specific types of testing performed at the facility (e.g. “analytical testing of drug substance” is not a sufficient description of the type of testing performed)

If this information is not provided on the 356h and its continuation pages, the applicant will be notified and given 5 U.S. business days to submit a corrected 356h. If this is not received within the provided 5 U.S. business days, the ANDA will be Refused for Receipt.
Module 1: Administrative (cont.)

  - If the proposed labeling is not consistent with a provided MOU Statement or patent certification, the applicant will be notified only that a change needs to be made. **If updated labeling is not submitted, or the Statement withdrawn, within 5 U.S. business days, the ANDA will be Refused for Receipt**

- Basis of Submission (BOS)
  - If a non-RLD listed drug is cited as a BOS, the applicant will be notified of the error. **A correction to the ANDA’s BOS must be received within 5 U.S. business days or the ANDA will be Refused for Receipt**
Module 3: Drug Substance (3.2.S)

- (a)(3)(F) applications

- Any deficiencies revealed in the API review will be communicated to the applicant by the filing reviewer. If a response is not received within 5 U.S. business days, the ANDA will be Refused for Receipt
Module 3: Drug Substance (3.2.S)  
-Type II API DMFs

744(B)(g)(2)(B)(i) of the Act:

An ANDA that references, by letter a letter of authorization, a Type II API DMF that has not been deemed available for reference shall not be received within the meaning of section 505(j)(5)(A).
What does this mean for you?
Module 3: Drug Substance (3.2.S)
-Type II API DMFs (cont.)

The time frame between the date of submission of a Type II API DMF and its “accompanying” ANDA submission was analyzed for approximately 75 NCE-1 submissions.

- Only 30% of these API DMFs were submitted beyond 60 days prior to the ANDA submission
- 38% were submitted within 30 days of the ANDA submission
- Of the 38% subset above, 43% were submitted within 10 days of the ANDA submission!
The trend needs to be reversed, so that ample time is allowed for the Initial Completeness Assessment determination to be made and any identified deficiencies addressed, all prior to the ANDA submission, to ensure that the Type II API DMF is determined to be available for reference at the time of receipt (refer to 744B(a)(2)(D)(ii)(II) of the Act).

Otherwise…
Module 3: Drug Substance (3.2.S)  
-Type II API DMFs (cont.)

the ANDA will be Refused for Receipt, if the referenced Type II API DMF is not on FDA’s Available for Reference list* at the time a receipt decision is to be made.  

Therefore, our best practice recommendation is that a Type II API DMF be submitted **at least 6 months** in advance of the ANDA submission.
Module 3: Drug Product

**Microbiology** (3.2.P.3.5)

- PBP Sterility Assurance Summary Table *(Refuse to Receive)*
  

  Place this table in Module 1, Section 1.14.1.4

- Additional Validation Studies *(Refuse to Receive)*
  
  - Terminally sterilized drug products
  - Aseptically filled drug products

- Floor plan of manufacturing facilities to confirm continuity of sterile environment
New stability guidelines as per the Stability Guidance and Q&A to be implemented on:

June 20, 2014
• ANDA Filing Checklist is Updated Quarterly (typically Mar-Jun-Sept-Dec)
• Revisions are driven by updated recommendations/guidances pertaining to the technical reviews that are conducted by the different disciplines within OGD
• Revisions may reflect future changes but are incorporated to provide applicants with ample notice
• A copy of the most recent edition of the checklist may be found at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM151259.pdf
• It would be prudent to use the checklist as a QC tool to ensure that all components of the submission are accounted for and easily accessed. An electronic copy of the ANDA Filing Checklist (if used) with active hyperlinks to each component should be placed in section 1.2, following the cover letter.
RSB Review Team
Iain Margand, Branch Chief

• Kojo Awuah
• Peter Chen
• Rebekah Granger
• Shannon Hill
• Jackie Lee Hoffman
• Tim Jetton
• Julia Lee

• Molly MacDonnell
• Kevin Ninan
• Ted Palat
• Susan Polifko
• Linh Vo
• Johnny Young
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The End

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