An Overview of the Draft Guidance *ANDA Submissions—Refuse-to-Receive Standards*

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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Draft guidance was published on Sept. 30, 2013 **(FDA/2013-D-1120)**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—General Considerations* (2003)

-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 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM364105.pdf)
- Table 5 (dissolution summary) should be included for all media/studies and for <u>all strengths</u>

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 <u>one</u> 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.)

Correct SAS Submission (Concentration Data):

Unit	Subj	Seq	Per	Trt	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Plasma	1	AB	1	A	0.000	0.000	21.234	43.312	55.543	38.856	39.024	41.507	35.169	35.438
Plasma	1	AB	2	B	0.000	1.411	38.019	54.489	52.785	46.432	45.030	45.518	41.647	38.291
Plasma	2	BA	1	B	0.000	0.000	1.728	3.199	6.985	11.417	25.004	26.239	26.332	24.331
Plasma	2	BA	2	A	0.000	0.000	0.000	12.610	44.830	59.591	53.561	38.419	37.205	33.782
Plasma	3	BA	1	B	0.000	0.000	0.000	3.539	14.835	21.128	30.463	29.994	28.269	30.005
Plasma	3	BA	2	A	0.000	2.428	17.132	34.059	35.055	28.367	34.561	30.210	37.564	35.825
Plasma	4	AB	1	A	0.000	4.691	30.028	29.579	40.665	32.385	40.845	37.459	32.542	35.154
Plasma	4	AB	2	B	0.000	0.000	15.452	24.051	33.312	46.312	49.517	40.661	37.870	34.680
Plasma	5	AB	1	A	0.000	3.414	15.907	27.841	30.892	32.123	35.559	36.471	35.700	30.464
Plasma	5	AB	2	B	0.000	2.334	9.327	22.143	28.869	32.461	35.960	35.811	34.143	32.242
Plasma	6	BA	1	B	0.000	0.000	7.004	34.578	33.558	31.013	33.779	31.558	31.983	31.556
Plasma	6	BA	2	A	0.000	0.000	0.000	4.741	27.882	38.988	29.734	23.763	25.549	28.048
Plasma	7	BA	1	B	0.000	0.000	2.339	15.321	45.203	51.512	47.121	40.892	43.763	35.929
Plasma	7	BA	2	A	0.000	0.000	34.373	52.759	43.878	45.464	41.433	36.502	35.618	31.412
Plasma	8	AB	1	A	0.000	0.000	4.340	23.619	30.389	32.735	33.232	34.791	28.853	30.353
Plasma	8	AB	2	B	0.000	0.000	3.325	16.968	27.795	41.924	38.591	31.392	32.382	32.224
Plasma	9	BA	1	B	0.000	1.879	32.094	44.227	41.865	38.357	35.504	33.174	34.658	34.376
Plasma	9	BA	2	A	0.000	1.654	42.910	41.759	46.417	41.571	39.218	35.443	34.976	34.316
Plasma	10	BA	1	B	0.000	0.000	5.941	43.673	36.334	29.513	24.414	17.651	18.744	17.374
Plasma	10	BA	2	A	0.000	0.000	22.215	45.715	41.638	37.463	31.630	28.073	26.783	25.322
Plasma	11	AB	1	A	0.000	3.676	49.620	70.391	50.549	42.738	38.431	36.603	32.995	30.708
Plasma	11	AB	2	B	0.000	1.991	52.322	64.840	50.342	46.509	43.070	39.796	38.104	36.467
Plasma	12	AB	1	A	0.000	0.000	13.529	18.300	30.424	28.860	26.054	22.857	19.620	23.556
Plasma	12	AB	2	B	0.000	0.000	10.991	47.576	47.148	39.662	36.683	29.034	28.529	27.829

Module 5: Clinical Study Reports (cont.)

Incorrect SAS Submission (Concentration Data):

SUBJECT	SEQ	FORM	PERIOD	TIME	CONC
1	RT	R	1	0	0
1	RT	R	1	0.25	5.706
1	RT	R	1	0.5	21.779
1	RT	R	1	0.75	46.904
1	RT	R	1	1	48.806
1	RT	R	1	1.25	57.817
1	RT	R	1	1.5	55.835
1	RT	R	1	1.75	42.098
1	RT	R	1	2	46.162
1	RT	R	1	2.25	42.25
1	RT	R	1	2.5	39.175
1	RT	R	1	2.75	37.469
1	RT	R	1	3	32.403
1	RT	R	1	3.25	28
1	RT	R	1	3.5	21.056
1	RT	R	1	3.75	24.262
1	RT	R	1	4	25.11
1	RT	R	1	4.5	25.273
1	RT	R	1	5	27.037
1	RT	R	1	6	16.425
1	RT	R	1	7	12.219
1	RT	R	1	8	8.37
1	RT	R	1	10	5.856
1	RT	R	1	12	3.44

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.)

- MOU Patent Statements (505(j)(2)(A)(viii) & 21 CFR 314.94(a)(12)(iii)) and Proposed Labeling
- 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!

Module 3: Drug Substance (3.2.S)

-Type II API DMFs (cont.)

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.

(*http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.pdf)

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)**

(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM352612.pdf)

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

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- Kojo Awuah
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- Shannon Hill
- Jackie Lee Hoffman
- Tim Jetton
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The End

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