ANDA Submissions – Amendments and Requests for Final Approval to Tentatively Approved ANDAs

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2019
Generics

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ANDA Submissions – Amendments and Requests for Final Approval to Tentatively Approved ANDAs Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist applicants in preparing and submitting amendments to tentatively approved abbreviated new drug applications (ANDAs), including requests for final approval. This guidance provides recommendations on the timing and content of amendments to tentatively approved ANDAs to facilitate submission in a timely fashion to enable final approval on the the earliest date on which the ANDA may lawfully be approved based on patent and/or exclusivity protections ("earliest lawful ANDA approval date").

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. ANDA Approval Pathway

The process for obtaining approval to market an innovator drug approved under a new drug application (NDA) differs from that for obtaining approval to market a generic drug under an ANDA. A sponsor of an innovator drug must submit an NDA, which must contain, among other things, a demonstration of the safety and effectiveness of the drug for the conditions of use for which approval is sought.[2]

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(1)).

To obtain approval of a generic drug, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of that generic drug. Instead, the applicant may rely on FDA's finding that the reference listed drug (RLD)[3] relied upon by the ANDA applicant is safe and effective. The ANDA applicant must identify the RLD on which it seeks to rely and, among other things, demonstrate, that the proposed generic drug product and the applicable RLD are the same with respect to their active ingredient(s), dosage form, route of administration, strength, previously approved conditions of use, and labeling (with certain exceptions).[4] An ANDA must also include sufficient information (1) to demonstrate that the proposed product is bioequivalent to the RLD[5] and (2) to ensure the product's identity, strength, quality, and purity.[6]

B. Patent Certifications and Exclusivities – Effect on Timing of ANDA Approval

The timing of ANDA approval depends on, among other things, the patent and/or exclusivity protections for the RLD. An NDA applicant must submit information in its application for each patent that claims the drug that is the subject of the NDA or that claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted against a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.[7] Upon approval of an NDA, FDA publishes certain patent information provided by the NDA holder in its publication *Approved Drug Products With Therapeutic Equivalence Evaluations*, known as the *Orange Book*.[8] An ANDA applicant must provide, in its ANDA, information related to any patents for the RLD in the Orange Book. In particular, the ANDA applicant generally must submit to FDA one of four specified certifications regarding the patents for the RLD under section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)(2)(A)(vii)).

If the Orange Book does not list a patent for the RLD that, in the opinion of the ANDA applicant and to the best of its knowledge, claims the RLD or that claims a use of such listed drug for which the applicant is seeking approval, the ANDA applicant must certify that such patent information has not been submitted by the NDA holder for listing in the Orange Book (a paragraph I certification).[9]

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[3] An RLD is the listed drug identified by FDA as the drug product on which an ANDA applicant relies in seeking approval of its ANDA. 21 CFR 314.3(b).

[4] See section 505(j)(2)(A) and 505(j)(4) of the FD&C Act and 21 CFR 314.94 and 21 CFR 314.127.

[5] See section 505(j)(2)(A)(iv) and 505(j)(4)(F) of the FD&C Act and 21 CFR 320.21(b).

[6] Section 505(j)(4) of the FD&C Act.

[7] Id. See also section 505(c)(2) of the FD&C Act.

[8] The Orange Book is available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[9] 21 CFR 314.94(a)(12)(i)(A). If, in the opinion of the ANDA applicant and to the best of its knowledge, there are no patents claiming the drug product, drug substance, or method of use of the drug product, the applicant must submit to its ANDA a certification stating that opinion. 21 CFR 314.94(a)(12)(ii).

With respect to each patent listed in the Orange Book for the RLD, the applicant's patent certification must state one of the following:

- That such patent has expired (a paragraph II certification)
- The date on which such patent will expire (a paragraph III certification)
- That such patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (a paragraph IV certification).[10]

If an applicant submits a paragraph I or II certification, the patent in question will not delay ANDA approval. If an applicant submits a paragraph III certification, the applicant agrees to wait until the relevant patent has expired before seeking final approval of its ANDA. If, however, an applicant wishes to seek approval of its ANDA ***before*** a listed patent has expired by challenging the validity of that patent, by claiming that the patent would not be infringed by the generic drug product proposed in the ANDA, or by claiming that the patent is unenforceable, the applicant must submit a paragraph IV certification to FDA.[11]

An applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder and each patent owner with notice of its paragraph IV certification, including a description of the legal and factual basis for the ANDA applicant's assertion that the patent is invalid, unenforceable, or will not be infringed.[12] If a patent is listed at the time an ANDA is submitted and, in response to notice of a paragraph IV certification, the NDA holder or patent owner initiates a patent infringement action against the ANDA applicant within 45 days of receiving the required notice, approval of the ANDA generally will be stayed for 30 months from the later of the date of receipt of the notice by any owner of the patent or the NDA holder or such shorter or longer time as the court might order.[13] If a patent is listed in the Orange Book after an ANDA is submitted but before the ANDA is approved, the applicant for the pending ANDA generally must amend its application and provide an appropriate patent certification or statement to the newly listed patent; however, a 30-month stay would not be available if the applicant submits a paragraph IV certification to the newly listed patent and the NDA holder or patent owner files a patent infringement action within 45 days of receipt of notice of the paragraph IV certification.[14]

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[10] Section 505(j)(2)(A)(vii) of the FD&C Act; see also 21 CFR 314.94(a)(12)(i)(A).

[11] The FD&C Act describes only one circumstance in which an ANDA applicant does not need to certify to a listed patent. Specifically, when a patent is listed only for a method of use, an ANDA applicant seeking to omit that approved method of use from the generic drug's labeling can submit a "section viii statement" that acknowledges that patent information has been submitted to FDA for a patent claiming a given method of use, but states that the patent at issue does not claim a use for which the applicant seeks approval. See section 505(j)(2)(A)(viii) of the FD&C Act. See also 21 CFR 314.94(a)(12)(iii).

[12] Section 505(j)(2)(B) of the FD&C Act.

[13] Section 505(j)(5)(B)(iii) of the FD&C Act and 21 CFR 314.107(b)(3)(i).

[14] Id. See also 21 CFR 314.94(a)(12)(vi).

The statute provides an incentive and a reward to generic drug applicants that expose themselves to the risk of patent litigation. The statute does so by granting a 180-day period of exclusivity *vis-à-vis* certain other ANDA applicants to the applicant that is first to file a substantially complete ANDA containing a paragraph IV certification to a listed patent.[15] In addition, the FD&C Act provides for a number of exclusivities for RLDs that can affect the timing of final approval of an ANDA.[16]

C. Tentative Approval and Amendments to Tentatively Approved ANDAs

If an ANDA meets the substantive requirements for approval but cannot be finally approved by FDA because of unexpired patents or exclusivities as described above, FDA will tentatively approve the ANDA. *Tentative approval* (TA)

> is notification that an NDA or ANDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved because there is a 7-year period of orphan exclusivity for a listed drug under section 527 of the [FD&C Act] and [21 CFR] 316.31… or that a 505(b)(2) application or ANDA otherwise meets the requirements for approval under the FD&C Act, but cannot be approved until the conditions in 314.107(b)(1)((iii), (b)(3), or (c) are met; because there is a period of exclusivity for the listed drug under 314.108; because there is a period of pediatric exclusivity for the listed drug under section 505A of the [FD&C Act]; because there is a period of exclusivity for the listed drug under section 505E of the [FD&C Act]; or because a court order pursuant to 35 U.S.C. 271(e)(4)(A) orders that the NDA or ANDA may be approved no earlier than the date specified. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval letter after any necessary additional review of the NDA or ANDA.[17]

Under section 505 of the FD&C Act, a drug product that is the subject of a tentatively approved ANDA is not an approved drug and may not be marketed without final Agency approval.[18]

An ANDA applicant may submit amendments to a tentatively approved application that propose changes to the application, request final approval, or propose changes *and* request final approval. As explained in this draft guidance, an amendment may delay FDA's final approval of the

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[15] See section 505(j)(5)(B)(iv)(I), 505(j)(5)(B)(iv)(II)(aa), and 505(j)(5)(D)(iii) of the FD&C Act.

[16] See section C for the definition of tentative approval, which includes a listing of the exclusivities that affect the timing of final approval of an ANDA.

[17] 21 CFR 314.3(b). See also section 505(j)(5)(B)(iv)(II)(dd)(AA) of the FD&C Act.

[18] See 21 U.S.C. 355(j)(5)(B)(iv)(II)(dd)(BB) (stating that a "drug that is granted [TA] by the Secretary is not an approved drug and shall not have an effective approval until the Secretary issues an approval after any necessary additional review of the application"); see also 21 CFR 314.105(d). In addition, under section 301 of the FD&C Act (21 U.S.C. 331), the introduction or delivery for introduction into interstate commerce of such a drug product before the final approval date is prohibited.

ANDA until after the earliest lawful ANDA approval date, depending on the nature of the changes proposed in the amendment and any related deficiencies identified upon review. This draft guidance is intended to assist applicants in preparing an amendment for submission in a timely fashion to obtain final approval on the earliest lawful approval date. In particular, applicants that wish to request final approval should determine whether changes are necessary before requesting this final approval, review any changes that have been made to their application since the TA was granted (see section V of this draft guidance), and consider the possible review goal dates that may be assigned to the request for final approval to request final approval in a timely fashion.

III. AMENDMENTS TO TENTATIVELY APPROVED ANDAs

A. Review Goals for Amendments Other Than Requests for Final Approval

There are several types of amendments that can be submitted after an ANDA receives TA. The GDUFA[19] Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter)[20] describes in general terms the review goal dates for the different amendment types, and FDA has provided additional information and recommendations related to these different types in its guidance for industry *ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA* (Amendments Guidance). Relevant to this discussion, if an applicant submits an amendment to its ANDA (1) after the ANDA has received TA but (2) before the applicant submits a request for final approval, the amendment will, in general, receive a review goal date consistent with the criteria outlined in the Amendments Guidance. For example, if an applicant submits an amendment adding a new facility, FDA will classify that amendment as a *major amendment* requiring preapproval inspection and set a 10-month review goal for that amendment. However, as described in the Amendments Guidance, FDA also may defer assessment of an amendment other than a request for final approval if the earliest lawful final approval date for that ANDA is not for several years. For example, FDA may defer assessment of a labeling update to an ANDA with paragraph III certifications to patents that will not expire for several years.[21]

To note, FDA will not delay assessment of amendments to ANDAs submitted and tentatively approved under the President's Emergency Plan for AIDS Relief (PEPFAR). Under PEPFAR, certain antiretroviral products that have been granted a TA may be distributed for use outside of the United States, even when there is still patent and/or exclusivity protection in the United States. For such products, FDA will set a goal date for assessing amendments to PEPFAR ANDAs consistent with the criteria outlined in the Amendments Guidance.

[19] *GDUFA* refers to the generic drug user fee program codified in the Generic Drug User Fee Amendments of 2012 and the Generic Drug User Fee Amendments of 2017.

[20] The GDUFA II Commitment Letter is available at https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf.

[21] See Amendments Guidance at 15.

B. Status of a Tentatively Approved ANDA Upon Submission of an Amendment

When an applicant submits an amendment to a tentatively approved ANDA, FDA will determine whether to assess that amendment or defer it, as described above. If the Agency decides to assess the amendment, FDA will convert the status of the ANDA from *TA* to *under review*; that internal designation will remain until FDA takes an action on the amendment. If FDA defers the amendment, the ANDA will remain in TA status until FDA assesses that amendment. If after assessment of the amendment, FDA determines that the ANDA meets all the requirements for TA or final approval, FDA will reissue the TA or grant a final approval, as appropriate. If FDA identifies deficiencies that have not been resolved during assessment of the amendment that are communicated in a complete response letter (CRL), the ANDA's status will be converted to *complete response* status until (1) the applicant adequately addresses the deficiencies identified in the CRL in a subsequent amendment and (2) FDA reissues a TA or grants final approval, as appropriate.

IV. SUBMISSION OF AND REVIEW GOALS FOR REQUESTS FOR FINAL APPROVAL

A. Requests for Final Approval

Only a drug product that is the subject of an ANDA with final approval may be lawfully marketed.[22] FDA does not automatically grant final approval upon the expiration of any periods of exclusivity or patent protection that served as the basis of the TA.[23] As described in FDA's regulations:

> A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval after any necessary additional review of the ANDA. FDA's tentative approval of a drug product is based on information available to FDA at the time of the tentative approval letter (*i.e.*, information in the ANDA and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to FDA's attention. A new drug product may not be marketed until the date of approval.[24]

[22] See note 18.

[23] FDA may act upon an amendment by granting final approval absent a formal request from the applicant if: (1) an ANDA applicant submits an amendment to a tentatively approved application, as described in section III of this draft guidance, and (2) upon conclusion of FDA's assessment of that amendment, that ANDA is determined to be eligible for final approval.

[24] 21 CFR 314.105(d).

Accordingly, an applicant with an ANDA in TA status generally submits an amendment to its ANDA explicitly requesting final approval to market its drug product.[25] All requests for final approval are considered *amendments* to the application. In general, these amendments will be classified as *major* or *minor* and assessed by FDA consistent with the criteria for review goal dates described in the Amendments Guidance. It is, therefore, incumbent on the applicant to accurately plan the timing of its request for final approval.

If an applicant is seeking final approval of an ANDA for which the applicant has provided a paragraph III certification, FDA recommends the applicant submit the request for approval 15 months before the earliest lawful ANDA approval date.[26] The two following subsections provide recommendations to ANDA applicants for submitting a request for final approval based on when TA was granted, in particular for applicants who provided paragraph IV certifications. However, regardless of when TA was granted, if an ANDA applicant submits a request for final approval that contains no new data, information, or other changes to the ANDA less than 3 months from the earliest lawful ANDA approval date but (1) could have identified the earliest lawful ANDA approval date and (2) failed to submit a timely standard request for final approval, the ANDA applicant risks the application not being approved by that date.

B. Applications with Paragraph IV Certifications Granted TA Status Less Than 3 Years Before the Earliest Lawful Approval Date

If an ANDA received a TA less than 3 years before the earliest lawful approval date, FDA recommends that the ANDA applicant submit an amendment with enough time to permit FDA to assess that amendment before the date on which the applicant seeks approval (e.g., the earliest lawful ANDA approval date). An applicant also should clearly identify, in its cover letter, that the amendment is a request for final approval. A request for final approval that contains no new data, information, or other changes to the ANDA is considered a *minor amendment*. FDA generally assesses these minor amendments within 3 months. Accordingly, ANDA applicants should submit such a request for final approval as a minor amendment no later than 3 months before the date on which the applicant is seeking final approval.

A request for final approval that contains substantive changes to an ANDA will be classified as a *major* or *minor amendment* based on the content in the request for final approval and will be assigned a review goal date that corresponds with that classification, as articulated in the Amendments Guidance. For example, a request for final approval that includes changes to include a new facility or a notification that there was a change in the status of the current manufacturing and testing facilities' compliance with current good manufacturing practices, both of which may require an inspection, could receive a goal date consistent with a major amendment in which an inspection is required (i.e., 10 months from the date of submission).

[25] 21 CFR 314.107(b)(4).

[26] This timeframe is recommended because the long period that oftentime exists between TA of an ANDA containing a Paragraph III certification and expiration of the relevant patent may necessitate a more extensive assessment of the ANDA.

C. Applications with Paragraph IV Certifications Granted TA Status 3 or More Years Before the Earliest Lawful Approval Date

If an ANDA has been in TA status for 3 or more years before the earliest lawful approval date, the lengthy passage of time since the TA may necessitate a more extensive assessment of the ANDA before final approval may be granted. For example, the applicable product-specific guidance for the ANDA may have been revised; manufacturing standards may have changed; or significant RLD labeling changes may have been approved. Therefore, FDA recommends that the ANDA applicant submit the request for final approval as a major amendment.[27] Submission of the request as a major amendment allows FDA to: (1) assess any changes that have been made since the application was granted TA, (2) complete any necessary inspection(s) of the ANDA's referenced facilities, and (3) grant final approval on the earliest lawful approval date. This amendment should be submitted 10 months before the earliest lawful approval date, as described further in the Amendments Guidance.[28]

D. Complete Responses and Reissued Tentative Approvals in Response to Requests for Final Approval

As described in section III.B of this draft guidance, if FDA identifies deficiencies in the request for final approval that are not addressed by an ANDA applicant during assessment and communicates those deficiencies in a CRL, the ANDA will be placed in *complete response* status until the deficiencies are adequately addressed by the applicant in a subsequent amendment. An applicant that receives a CRL must adequately address the deficiencies before FDA may reissue the TA or grant final approval, as applicable.

FDA may reissue a TA in response to a request for final approval of a tentatively approved ANDA if a review goal date is set for before the earliest lawful approval date. For example, FDA may reissue the TA if (1) an applicant submits the request in advance of the time it will take FDA to assess the amendment under the applicable GDUFA review goals and (2) FDA does not identify any deficiencies in the request. Alternatively, if appropriate, FDA may choose to miss a review goal date and grant final approval on the earliest lawful approval date if that date is imminent. If FDA reissues the TA, the applicant should submit a new request for final approval per the recommendations outlined in this draft guidance.

V. POST-TA CHANGES THAT MAY IMPACT FINAL APPROVAL

FDA has identified common developments that may require an applicant to make changes that should be submitted in an amendment to its tentatively approved ANDA before final approval is

[27] Note that the Agency will evaluate the amendment upon submission to determine whether the amendment is *major* or *minor* and assign a goal date accordingly, but applicants should include a statement indicating that the request for final approval should be considered major. See Section VI of this guidance.

[28] In certain cases, an amendment may be designated as *priority* and subject to an 8-month review goal. See the Amendments Guidance and the draft guidance for industry *ANDAs: Pre-Submission of Facility Information Related to Prioritized Generic Drug Applications (Pre-Submission Facility Correspondence).* When final, the guidance will represent the FDA's current thinking on this topic.

granted. FDA is providing the following non-exhaustive list of these common developments to assist ANDA applicants in ensuring that their tentatively approved ANDA is complete and up-to-date before they request final approval.

Product Quality Updates

- New active pharmaceutical ingredient (API) source in a Type II API drug master file
- Scientific and technical changes to the product, process, analytical methods, and/or specifications
- New and/or updated United States Pharmacopeia (USP) chapters and/or monographs[29]
- Updated stability data
- New facilities
- Changes in the status of referenced facilities
- Changes to the size, shape, or color of a solid oral dosage form
- New test methods
- New submission batch data
- New certificates of analysis
- New packaging information (particularly for injectable products)
- New equipment or methods for sterilization and/or depyrogenation (for sterile drug products)
- Updates to drug master files

Bioequivalence Updates

- New in vivo or in vitro bioequivalence studies conducted consistent with recommendations in a newly issued, revised, or finalized product-specific guidance[30]

[29] The United States Pharmacopeia-National Formulary (USP-NF) is available at http://www.uspnf.com/.

[30] To facilitate generic drug product availability and to assist the generic pharmaceutical industry with (1) identifying the most appropriate methodology for developing drugs and (2) generating evidence needed to support ANDA approval, FDA publishes product-specific guidances describing the Agency's current thinking and expectations on how to develop generic drug products that are therapeutically equivalent to specific RLDs. Product-specific guidances are available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

Labeling Updates

- Changes to labeling to reflect approved changes to the labeling for the RLD
- Changes to labeling to reflect changes in new and/or updated USP chapters and/or monographs
- Changes to labeling to reflect new product quality information or information related to bioequivalence studies
- Changes to labeling to reflect an omission of an indication or other aspect of labeling protected by patent or exclusivity under the FD&C Act,[31] including labeling to reflect the *split* approval of an application (i.e., labeling to reflect final approval of only certain strengths of a drug product that were previously tentatively approved in the ANDA)
- Changes to labeling to reflect subsequently approved indications
- Changes to labeling to reflect statements previously carved out that are no longer protected by patent or exclusivity under the FD&C Act[32]
- Changes to containers, blisters, cartons, and other finished dosage form packaging
- New proprietary name requests or requests to reassess a proprietary name that had been conditionally granted

Orange Book Listing, Patent, and Exclusivity Updates

- Updated patent certification or statement (or a recertification for a previously submitted paragraph IV certification) with the types of amendments described in 21 CFR 314.96(d)(1) or a verification that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.96(d)(1)[33]

[31] See note 11. If an applicant submits a change in patent certification that may result in or otherwise requests a *carve-out* of any protected indications from the labeling to obtain final approval before the exclusivity for that protected indication expires, FDA's assessment of those carve-outs may require consultations to offices outside of the Office of Generic Drugs. If a consult is needed, FDA may need additional assessment time. Therefore, applicants should be aware that carve-out assessments may require more assessment time than the assessment time allotted for a minor amendment.

[32] If an ANDA applicant submits an amendment seeking approval for a subsequently approved indication or other condition of use that is protected by patent, the applicant would need to submit an appropriate patent certification or statement in the amendment.

[33] See 21 CFR 314.96(d).

- An appropriate patent certification or statement to a timely filed, newly listed patent for the RLD

- Changes in a patent certification (e.g., a change from a paragraph IV to a paragraph III certification)[34]

- Litigation updates (e.g., notification of court actions or written consent to approval[35])

- Confirmation that the RLD is identified in the Active section of the Orange Book[36]

VI. CONTENT OF REQUESTS FOR FINAL APPROVAL

A request for final approval should clearly identify, in its cover letter, all changes to the ANDA that have been made since the TA was granted.[37] It is incumbent on the ANDA applicant (1) to monitor for updates related to the applicant's drug product (e.g., new, revised, or finalized product-specific guidances; RLD labeling changes or updates; or USP changes or updates) and (2) to ensure that amendments addressing these updates are timely submitted to and are clearly identified for FDA either before a request for final approval (i.e., in a post-TA amendment) or in the request for final approval amendment itself, permitting FDA sufficient assessment time to meet the ANDA's earliest lawful approval date (see sections III and IV of this draft guidance).

Applicants should submit a complete and accurate Form FDA 356h[38] with their request for final approval. Additionally, FDA recommends that requests for final approval indicate all of the following:

- If there has been no change to the ANDA between FDA's issuance of the TA and the applicant's request for final approval, the applicant should clearly state that there has been no change to the ANDA.

- If editorial or other nonsubstantive changes have been made to the ANDA between FDA's issuance of the TA and the applicant's request for final approval, the request for final approval should clearly state what those changes were and identify where, in the ANDA, those changes were made.

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[34] See note 11.

[35] See 21 CFR 314.107(e).

[36] When an RLD is moved to the Discontinued section of the Orange Book, that RLD remains a *listed drug* (see 21 CFR 314.3(b)) and is available for reference by an ANDA applicant unless FDA makes a determination that the RLD was withdrawn from sale for reasons of safety or effectiveness. Under 21 CFR 314.161(a), such a determination can be made by FDA at any time, but FDA must make this determination before approving an ANDA that refers to the listed drug.

[37] FDA also recommends that applicants requesting final approval list all amendments submitted to FDA for assessment after the TA.

[38] Form FDA 356h is available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm.

- If the ANDA contains substantive new information since FDA's issuance of the TA, the request for final approval should clearly identify the new information, the changes that have been made, and the location of information supporting these changes in the ANDA. The request for final approval should also contain, for FDA's assessment of that request, supporting information commensurate with that change.

- If the labeling for the proposed drug product has changed, as compared to the labeling submitted with the original ANDA, applicants should include a side-by-side labeling comparison of their proposed labeling with their last submission and/or the current RLD labeling. This comparison should annotate any differences and explain any changes that have been made, including those made because of updates in product quality or bioequivalence information.

- A statement indicating whether the request for final approval should be considered *major* or *minor* consistent with the criteria outlined in the Amendments Guidance.