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

Guidance for Industry

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

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Generic Drugs

Revision 2

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Contains Nonbinding Recommendations

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

This guidance represents 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 office 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 earliest date on which the ANDA may lawfully be approved based on patent and/or exclusivity protections ("earliest lawful ANDA approval date").

This guidance replaces the final guidance of the same title issued in January 2024. This guidance contains clarifying revisions to section II.C, section IV, and section VI concerning amendments to tentatively approved ANDAs and the timing of those amendments.

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

The Generic Drug User Fee Amendments of 2012 (GDUFA I)[2] amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to authorize FDA to assess and collect user fees to provide the Agency with resources[3] to help ensure patients have access to quality, safe, and effective

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) at FDA. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2017-D-6821 (available at https://www.regulations.gov/docket?D=FDA-2017-D-6821). See the instructions in that docket for submitting comments on this and other Level 2 guidances.

[2] Title III of the Food and Drug Administration Safety and Innovation Act, Public Law 112-144.

[3] User fees are available for obligation in accordance with appropriations acts.

generic drugs. GDUFA[4] fee resources bring greater predictability and timeliness to the review of generic drug applications. GDUFA has been reauthorized every 5 years to continue FDA's ability to assess and collect GDUFA fees, and this user fee program has been reauthorized two times since GDUFA I, most recently in the Generic Drug User Fee Amendments of 2022.[5] As described in the Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (GDUFA III commitment letter) applicable to this latest reauthorization, FDA has agreed to performance goals and program enhancements regarding aspects of the generic drug assessment program that build on previous authorizations of GDUFA.[6] New enhancements to the program are designed to maximize the efficiency and utility of each assessment cycle, with the intent of reducing the number of assessment cycles for ANDAs and facilitating timely access to generic medicines for American patients.

A. ANDA Approval Pathway

The process for obtaining approval to market a drug product approved under a new drug application (NDA) differs from that for obtaining approval to market a generic drug under an ANDA. A sponsor[7] 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.[8]

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 relies on FDA's finding that the reference listed drug (RLD)[9] 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, conditions of use, and labeling (with certain permissible exceptions).[10] An ANDA must also include sufficient information to (1) demonstrate that the proposed product is bioequivalent to the RLD[11] and (2) ensure the product's identity, strength, quality, and purity.[12]

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

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[4] GDUFA refers to the generic drug user fee program codified in the Generic Drug User Fee Amendments of 2012, the Generic Drug User Fee Amendments of 2017, and the Generic Drug User Fee Amendments of 2022.
[5] Enacted as Title III of Division F (the FDA User Fee Reauthorization Act of 2022) of the Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023 (Public Law 117-180).
[6] The GDUFA III commitment letter is available at https://www.fda.gov/media/153631/download.
[7] The term *sponsor* and the term *applicant* are used interchangeably in this guidance to refer to any person who submits an NDA or ANDA, or an amendment or supplement to an NDA or ANDA, and any person who owns an approved NDA or ANDA.
[8] Section 505(b)(1) of the FD&C Act (21 U.S.C. 355(b)(1)).
[9] 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).
[10] 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.
[11] See section 505(j)(2)(A)(iv) and 505(j)(4)(F) of the FD&C Act and 21 CFR 320.21(b).
[12] Section 505(j)(2)(A)(vi) and 505(j)(4)(A) of the FD&C Act.

protections for the RLD. Not later than 30 days after the date of approval of an NDA, the NDA applicant must submit certain information to FDA for each patent that claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent, or that claims a method of using such drug for which approval has been granted in the NDA, and for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug.[13] FDA publishes (or "lists") certain patent information submitted by the NDA holder under section 505(c) of the FD&C Act in its publication *Approved Drug Products With Therapeutic Equivalence Evaluations*, known as the *Orange Book.*[14] An ANDA must contain an appropriate patent certification for each patent that claims the RLD or a method of using the RLD for which the ANDA applicant seeks approval in its ANDA and for which the NDA applicant is required to submit information.[15] In particular, the ANDA applicant generally must submit to FDA one of four specified certifications regarding such patents, under section 505(j)(2)(A)(vii) of the FD&C Act (21 U.S.C. 355(j)(2)(A)(vii)):

- That such patent information has not been filed (a paragraph I certification)
- 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).[16]

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 final 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.[17]

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.[18] If a patent is listed at the time an ANDA is submitted and, in response to notice of a paragraph IV certification, the patent owner or its representative or the exclusive patent licensee initiates a patent infringement action against the

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[13] Section 505(c)(2) of the FD&C Act.
[14] Section 505(j)(7)(A)(iii) of the FD&C Act. The Orange Book is available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.
[15] Section 505(j)(2)(A)(vii) of the FD&C Act and 21 CFR 314.94(a)(12)(i)(A).
[16] Section 505(j)(2)(A)(vii) of the FD&C Act; see also 21 CFR 314.94(a)(12)(i)(A).
[17] See 21 CFR 314.94(a)(12)(i)(A)(4). When a patent is listed only for a method of use, an ANDA applicant not seeking approval for that method of use 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. Section 505(j)(2)(A)(viii) of the FD&C Act. See also 21 CFR 314.94(a)(12)(iii)(A).
[18] Section 505(j)(2)(B) of the FD&C Act and 21 CFR 314.95(c).

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.[19] 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 result from an ANDA applicant submitting a paragraph IV certification to a patent for which the relevant patent information was submitted after the ANDA applicant submitted its application.[20]

The statute provides an incentive and a reward to generic drug applicants that expose themselves to the risk of patent litigation. It does so by making first applicants eligible for 180-day exclusivity vis-à-vis certain other ANDA applicants, known as *subsequent applicants*.[21] 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.[22]

C. Tentative Approval and Amendments to Tentatively Approved ANDAs

If an ANDA meets the substantive requirements for approval but cannot receive final approval from FDA due to patent or exclusivity reasons, 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.[23]

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 does not have an effective approval until FDA issues an approval after any necessary additional review of the application.[24] A drug product that is the subject of a tentatively approved ANDA may not be marketed without final Agency approval under section 505(j) of the FD&C Act. The introduction or delivery for introduction into

[19] Section 505(j)(5)(B)(iii) of the FD&C Act and 21 CFR 314.107(b)(3)(i).
[20] Ibid. See also 21 CFR 314.94(a)(12)(vi).
[21] See section 505(j)(5)(B)(iv)(I), 505(j)(5)(B)(iv)(II)(aa)-(cc), and 505(j)(5)(D)(iii) of the FD&C Act.
[22] See section II.C of this guidance for the definition of *tentative approval*, which includes a listing of the exclusivities that affect the timing of final approval of an ANDA.
[23] 21 CFR 314.3(b). See also section 505(j)(5)(B)(iv)(II)(dd)(AA) of the FD&C Act and 21 CFR 314.105(d).
[24] See section 505(j)(5)(B)(iv)(II)(dd)(BB); see also 21 CFR 314.105(d).

interstate commerce of such a drug product before the final approval date is prohibited under section 301 of the FD&C Act (21 U.S.C. 331). Until the Agency issues the final approval letter, such a drug product will not be deemed approved for marketing under section 505(j) of the FD&C Act, and will not be listed in the Orange Book.[25]

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 guidance, an amendment may delay FDA's final approval of the ANDA until after the earliest lawful ANDA approval date, depending on the timing of submission of the amendment and the nature of the changes proposed in the amendment and any related deficiencies identified upon review.[26] This 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 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 III commitment letter describes review goal dates for the different amendment types, and FDA has provided additional information and recommendations related to these different types of amendments in its guidance for industry *ANDA Submissions–Amendments to Abbreviated New Drug Applications Under GDUFA* (Amendments Guidance).[27] 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 review goal dates outlined in the GDUFA III commitment letter and described in the Amendments Guidance. For example, if an applicant submits a standard amendment adding a new facility requiring preapproval inspection, FDA will classify that amendment as a *major amendment* requiring preapproval inspection and set a 10-month review goal for that amendment.

As described in the Amendments Guidance, FDA also may, in limited situations, defer assessment of an amendment other than a request for final approval if the earliest lawful approval date for that ANDA is not for several years. For example, FDA may defer assessment

[25] Section 505(j)(7)(A)(iii) of the FD&C Act. The Orange Book is available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[26] We note that in addition to an amendment requesting final approval, the Agency may request, at any time prior to the date of final approval, that an ANDA applicant submit an additional amendment containing information as specified by the Agency. Failure to submit either or, if requested, both types of amendments may result in a delay in the issuance of the final approval letter.

[27] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

of a labeling update that does not require a change in patent certification for an ANDA with paragraph III certifications to patents that will not expire for several years.[28]

To note, FDA will not defer assessment of amendments to ANDAs that have been tentatively approved and are included in the President's Emergency Plan for AIDS Relief (PEPFAR).[29] 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 that reflects their distribution under that program and is consistent with the description in the Amendments Guidance.

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, for tracking purposes, FDA will convert the status of the ANDA in its internal systems 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 in FDA's internal systems 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 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 TA or grants final approval, as appropriate.

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

A. Requests for Final Approval

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.[30] As described in FDA's regulations:

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[28] For further discussion on FDA's practice of deferring assessment of certain amendments and when the Agency may defer assessment of an amendment to a tentatively approved ANDA, see Amendments Guidance at 13 and 14-15.

[29] See FDA's PEPFAR web page, available at https://www.fda.gov/international-programs/presidents-emergency-plan-aids-relief-pepfar.

[30] 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 guidance; and (2) upon conclusion of FDA's assessment of that amendment, that ANDA is determined to be eligible for final approval.

> 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.[31]

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.[32] 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 review goal dates outlined in the GDUFA III commitment letter and described in the Amendments Guidance. It is, therefore, incumbent on the applicant to accurately plan the timing of its request for final approval.

The two following subsections provide recommendations to ANDA applicants for submitting a request for final approval based on when TA was granted. As noted in this section, all requests for final approval, including those subject to changes in the relevant patent and exclusivity barriers to approval, are assigned goal dates consistent with the GDUFA performance goals.

B. Applications With Granted TA Status Less Than 3 Years Before 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 final 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 or references changes submitted in a prior amendment that was deferred by FDA 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 GDUFA III commitment letter and described in the Amendments Guidance.[33] For example, a request for final approval

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[31] 21 CFR 314.105(d).

[32] See 21 CFR 314.107(b)(4).

[33] ANDA applicants should review the Amendments Guidance to determine the duration of Agency review needed to assess the changes submitted. As part of this consideration, ANDA applicants should monitor any changes to the RLD that occur after TA, including changes in labeling, patent or exclusivity information, or marketing status (see sections V and VI of this guidance). The submission of multiple amendments prior to final approval may also result in a delay in the issuance of a final approval letter.

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 standard major amendment in which an inspection is required (i.e., 10 months from the date of submission).

C. Applications Granted TA Status 3 or More Years Before Earliest Lawful Approval Date

As noted above, 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 final approval (e.g., the earliest lawful ANDA 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, bioequivalence (BE) standards may have changed; product quality standards may have changed; or significant RLD labeling changes may have been approved (see section V of this guidance). Therefore, FDA recommends that the ANDA applicant consider the changes and updates made to the application since the TA was granted and submit the request for final approval as a minor or major amendment, as appropriate.[34] 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. Considering the possible review goal dates that may be assigned to the request for final approval, this amendment should be submitted no later than 10 months before the date on which the applicant seeks approval (e.g., the earliest lawful ANDA approval date), as described further in the Amendments Guidance.[35]

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

As described in section III.B of this 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.[36] An applicant that receives a CRL must adequately address the deficiencies before FDA may reissue TA or grant final approval, as applicable.[37]

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[34] 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 (see section VI of this guidance).

[35] In certain cases, a major amendment requiring preapproval inspection may be designated as *priority* and subject to an 8-month review goal where certain facility information is pre-submitted. See the GDUFA III commitment letter at Sections I.A.5.b. and XI.U. See also Amendments Guidance at 6-7 and the guidance for industry *ANDAs: Pre-Submission Facility Correspondence Related to Prioritized Generic Drug Submissions* (Pre-Submission Facility Correspondence) (2025).

[36] We note that FDA may communicate with the applicant, as appropriate, during assessment of the applicant's application.

[37] 21 CFR 314.110(b).

FDA may reissue 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 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 work through the goal date and grant final approval on the earliest lawful approval date if that date is imminent rather than reissuing TA on the goal date.[38] If FDA reissues TA, the applicant should submit a new request for final approval per the recommendations outlined in this guidance.

V. POST-TA CHANGES THAT MAY IMPACT FINAL APPROVAL

FDA has identified common developments that may result in an applicant making changes that should be submitted in an amendment to its tentatively approved ANDA before final approval is granted. FDA is providing the following nonexhaustive list of these common developments to assist ANDA applicants, as applicable, in ensuring that their tentatively approved ANDAs are complete and up-to-date before they request final approval. For these and other changes, FDA reminds applicants that they should consider whether the changes would be classified as major or minor, and then plan accordingly in determining when to submit such a request to ensure approval by the earliest lawful approval date.

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[39]
- 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

[38] See the GDUFA III commitment letter at Section II.B.3 ("FDA will continue assessment of an ANDA past the goal date if, in FDA's judgment, it may be possible to approve . . . an ANDA within 60 days after the goal date . . . [w]hen the application meets the requirements for tentative approval by the goal date, but the legally permissible ANDA approval date is within 60 days after the goal date, and FDA may be able to approve the ANDA when it becomes legally permissible to do so.").

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

- New submission batch data
- 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

BE Updates

- New in vivo or in vitro BE studies or other analyses, e.g., conducted consistent with recommendations in a newly issued, revised, or finalized product-specific guidance (PSG), if they are relevant to the ANDA and new data or analyses should be generated[40]

Labeling Updates

- Changes to labeling to reflect approved changes to the labeling for the RLD, including changes to the labeling to reflect subsequently approved indications
- 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 BE 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,[41] including labeling to reflect the *split* approval of an application (i.e., labeling to reflect final approval of only certain

[40] To facilitate generic drug product availability and to assist the generic pharmaceutical industry with: (1) identifying the most appropriate methodology for developing drugs (see 21 CFR 320.24); and (2) generating evidence needed to support ANDA approval (see 21 CFR 314.94(a)(7) and § 320.21(b)), FDA publishes PSGs describing the Agency's current thinking and recommendations on how to develop generic drug products that are therapeutically equivalent to specific RLDs. PSGs are available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm. We note that applicants can use an alternate approach if it satisfies the requirements of the applicable statutes and regulations, and that these alternate approaches, or questions about the PSG, may be submitted to an applicant's ANDA. Note that, under the GDUFA III commitment letter, when a new or revised PSG is published and an applicant or prospective applicant has already commenced an in vivo BE study (i.e., the study protocol has been signed by the study sponsor and/or the contract research organization) the applicant or prospective applicant may request a PSG Teleconference to obtain Agency feedback on the potential impact of the new or revised PSG on its development program. See the GDUFA III commitment letter at Section III.C.5.

[41] See footnote 18. If an applicant submits a change in patent certification that may result in or otherwise requests a *carve-out* of any protected indications or other conditions of use from the labeling to obtain final approval before the protection for that indication or other condition of use 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.

strengths of a drug that were previously tentatively approved, and labeling to reflect another TA of the remaining proposed strengths of a drug in the ANDA)

- Changes to labeling to reflect statements previously carved out that are no longer protected by patent or exclusivity under the FD&C Act[42]

- 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)[43]

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

- An appropriate exclusivity statement to address a new exclusivity for the RLD

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

- Litigation updates (e.g., notification of court actions or written consent to approval[44])

- Confirmation that the RLD is identified in the Active section of the Orange Book[45]

VI. CONTENT OF REQUESTS FOR FINAL APPROVAL

An amendment requesting final approval should be designated clearly in its cover letter as a "FINAL APPROVAL REQUESTED." The amendment should provide the legal/regulatory basis for the request for final approval and should include a copy of a court decision, settlement or licensing agreement, or other information described in 21 CFR 314.107, as appropriate. A

[42] 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 must submit an appropriate patent certification in the amendment and provide documentation of timely sending and receipt of notice, as appropriate. See 314.96(d)(1) and 314.95(e).

[43] See 21 CFR 314.96(d).

[44] See 21 CFR 314.107(e).

[45] 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 after the drug has been voluntarily withdrawn from sale, but FDA must make this determination before approving an ANDA that refers to the listed drug.

request for final approval should also clearly identify, in its cover letter, all changes to the ANDA that have been made since the TA was granted.[46] It is incumbent on the ANDA applicant to (1) monitor for updates related to the applicant's drug product (e.g., changes in BE recommendations or requirements; RLD labeling changes or updates; or USP changes or updates) and (2) 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 guidance).

Applicants should submit a complete and accurate Form FDA 356h[47] 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.

- 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, including any changes submitted in an amendment that was deferred by FDA. 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 BE information.

- The amendment classification (*major* or *minor*) proposed by the applicant consistent with the criteria outlined in the Amendments Guidance.

[46] FDA also recommends that applicants requesting final approval list all amendments submitted to FDA for assessment after the TA.
[47] Form FDA 356h is available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm.