ANDA Submissions – Prior Approval Supplements Under GDUFA

Guidance for Industry

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

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Generic Drugs

Revision 2

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10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
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Contains Nonbinding Recommendations

ANDA Submissions – Prior Approval Supplements Under GDUFA 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 preparing to submit to FDA prior approval supplements (PASs) and amendments to PASs for abbreviated new drug applications (ANDAs) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)). The guidance explains how the Generic Drug User Fee Amendments (GDUFA) relates to PAS submissions. The guidance revises the guidance of the same title issued in October 2017. This revision is being issued to incorporate the performance goals currently outlined in the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years [Fiscal Years [FYs]] 2023-2027 (GDUFA III commitment letter) that FDA has agreed to meet,[2] and clarifies how FDA will handle a PAS and amendments to a PAS for an ANDA subject to the performance goals in the GDUFA III commitment letter.

Specifically, this guidance describes how the GDUFA performance goals apply to:

- A PAS subject to the refuse-to-receive (RTR) standards
- A PAS that requires an inspection[3]
- A PAS for which an inspection is not required
- An amendment to a PAS
- Other PAS-related matters

[1] This guidance has been prepared by the Division of Policy Development in the Office of Generic Drug Policy in the Center for Drug Evaluation and Research at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2014-D-0901 (available at https://www.regulations.gov/docket/FDA-2014-D-0901).

[2] The performance goals were proposed jointly by FDA and representatives of the generic drug industry. See the GDUFA I commitment letter, available at https://www.fda.gov/media/82022/download, the GDUFA II commitment letter, available at https://www.fda.gov/media/101052/download, and the GDUFA III commitment letter, available at https://www.fda.gov/media/153631/download.

[3] Section 704 of the FD&C Act (21 U.S.C. 374) authorizes FDA to conduct inspections.

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 guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

The Generic Drug User Fee Amendments of 2012 (GDUFA I)[4] amended the FD&C Act to authorize FDA to assess and collect user fees to provide the Agency with resources[5] to help ensure patients have access to quality, affordable, safe, and effective generic drugs. GDUFA 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 FDA User Fee Reauthorization Act of 2022. As described in the 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. 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.

In the GDUFA III commitment letter, FDA committed to assess and act on a certain percentage of PASs within a specified period from the date of submission in FY 2023-2027. The applicable assessment goal depends on whether assessment of a PAS requires an inspection. As reflected in the GDUFA III commitment letter, FDA also agreed to certain performance goals that are carried over from the GDUFA II commitment letter.

GDUFA I established application fees (for ANDAs, PASs to ANDAs, and certain drug master files (DMFs)), annual facility fees, and a one-time fee for ANDAs that were pending on October 1, 2012 (referred to as "backlog applications"). As explained in the GDUFA II commitment letter, however, the Agency and industry agreed to the elimination of PAS fees. As of October 1, 2017, ANDA applicants are no longer required to pay application fees when they submit a PAS. Please note that Type II active pharmaceutical ingredient (API) DMF holders are still subject to a DMF fee the first time an initial letter of authorization references that DMF in an ANDA or PAS.[6]

III. IMPACT OF GDUFA PERFORMANCE GOALS ON PAS SUBMISSIONS

FDA regulations lay out requirements for making and reporting changes to approved ANDAs (see 21 CFR 314.70). Under the GDUFA III commitment letter, the generic drug industry and FDA have agreed to certain performance goals, including those applicable to PASs. This section

[4] Title III of the Food and Drug Administration Safety and Innovation Act, Public Law 112-144.
[5] User fees are available for obligation in accordance with appropriations acts.
[6] Procedures for ANDA and PAS submissions are set forth in FDA's regulations in part 314 (21 CFR part 314).

describes the specific performance goals that apply to PASs and amendments to PASs submitted to ANDAs.

The GDUFA performance goals do not apply to new drug applications (NDAs) or biologics license applications (BLAs). Nor do they apply to supplements filed for NDAs or BLAs, changes-being-effected (CBE) supplements and amendments to CBEs for ANDAs, or annual report filings to NDAs, BLAs, or ANDAs. In this guidance, any reference to a PAS refers only to a PAS filed for an ANDA, unless clearly indicated otherwise.

A. Changes to an Approved Application

Section 506A of the FD&C Act (which was added by section 116 of the Food and Drug Administration Modernization Act of 1997) provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes.[7] The following sections of FDA's regulations set forth the requirements for supplements and other changes to approved applications under section 506A:

- § 314.70 describes the different reporting categories for changes to an approved application.
- § 314.71 outlines the procedures for submitting a supplement to an approved application.
- § 314.97 provides that supplements and other changes to an approved ANDA must comply with the requirements of §§ 314.70 and 314.71.

Specifically, section 506A of the FD&C Act and § 314.70 of FDA regulations provide for the following reporting categories of changes to an approved application:

1. **Major Change**: a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. A major change requires the submission of a PAS and approval by FDA before distribution of the drug product made using the change.[8]

2. **Moderate Change**: a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. Depending on the nature of the change, one of the following two types of supplements must be submitted to FDA for a moderate change:

    a. **Supplement – Changes Being Effected in 30 Days (CBE-30 supplement)**: A CBE-30 supplement involves certain moderate changes that require the

[7] 21 U.S.C. 356a.

[8] § 314.70(b).

submission of the supplement to FDA at least 30 days before the distribution of the drug product made using the change.[9]

b. **Supplement – Changes Being Effected (CBE-0 supplement)**: A CBE-0 supplement involves certain moderate changes that allow distribution to occur as soon as FDA receives the supplement.[10]

3. **Minor Change:** a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. The applicant must describe minor changes in its next annual report.[11]

The criteria for submitting information as a PAS, as a CBE, or in an annual report were not changed by GDUFA.[12] This guidance does not discuss the various criteria that apply in determining the respective reporting categories for these supplements. For additional information on these reporting categories, refer to § 314.70, as well as related guidances, including but not limited to the *Scale-Up and Post-approval Changes (SUPAC)* guidances and the *Changes to an Approved NDA or ANDA* guidance.

Additionally, a comparability protocol submitted in a PAS to an ANDA for a specific drug product, once approved, may justify a reduced reporting category for the same change in subsequent supplements to that ANDA. For further information on a comparability protocol submitted in a PAS, see the draft guidance for industry *Comparability Protocols: Chemistry, Manufacturing, and Controls Information*.[13]

B. GDUFA Performance Goals for PAS Submissions

The GDUFA II commitment letter outlined the performance goals FDA agreed to for assessing and acting on PASs submitted in FY 2018 through FY 2022[14] and delineated between standard and priority PASs for performance purposes.[15] It further revised FDA's GDUFA performance

[9] § 314.70(c)(3).

[10] § 314.70(c)(6).

[11] § 314.70(d).

[12] In regard to submissions for modifications and revisions to approved risk evaluation and mitigation strategies (REMS), refer to the guidance for industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions* (June 2020). 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.

[13] When final, this guidance will represent the current thinking of FDA.

[14] The performance goals related to PASs and PAS Amendments appear on pages 66686-8 of the GDUFA II commitment letter.

[15] The GDUFA II and GDUFA III commitment letter define "priority" as "submissions affirmatively identified as eligible for expedited review pursuant to CDER's Manual of Policy and Procedures (MAPP) 5240.3, *Prioritization*

goals for amendments, eliminating the Tier system.[16] The performance goals for assessing and acting on PASs have not changed from the GDUFA II commitment letter to the GDUFA III commitment letter Specifically, under the GDUFA III commitment letter, FDA agreed to the goals outlined as follows:

Submission Type	Goal
Standard PASs	90% assessed and acted on within 6 months of submission date if preapproval inspection not required.
	90% assessed and acted on within 10 months of submission date if preapproval inspection required.
Priority PASs	90% assessed and acted on within 4 months of submission date if preapproval inspection not required.
	90% assessed and acted on within 8 months of submission date if preapproval inspection required and applicant meets requirements under section I(B)(2)(b) relating to submission of Pre-Submission Facility Correspondence (PFC).[17]
	90% within 10 months of submission date if preapproval inspection is required and applicant meets any limitations as described under section I(B)(2)(c) relating to submission of a PFC.[18]

Submission Type	Goal
Standard PAS Major Amendments	90% assessed and acted on within 6 months of submission date if preapproval inspection not required.
	90% assessed and acted on within 10 months of submission date if preapproval inspection required.
Priority PAS Major Amendments	90% assessed and acted on within 4 months of submission date if preapproval inspection not required.
	90% assessed and acted on within 8 months of submission date if preapproval inspection required and applicant meets requirements under section I(B)(4)(b) relating to submission of a PFC.

of the Review of Original ANDAs, Amendments and Supplements, as revised. See page 27 of the GDUFA II commitment letter and page 47 of the GDUFA III commitment letter.

[16] For more detail on how FDA intends to classify major and minor amendments to original ANDAs and PASs under GDUFA, see the guidance for industry *ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018).

[17] Under the GDUFA III commitment letter, the 8-month goal date is available to priority PASs requiring an inspection when the applicant submits a complete and accurate Pre-Submission Facility Correspondence (PFC) no later than 60 days prior to the date of the PAS submission and the PFC is found to be complete, accurate, and remain unchanged at the time of the PAS submission. See page 8 of the GDUFA III commitment letter.

[18] Under the GDUFA III commitment letter, the 10-month goal date is available to priority PASs requiring an inspection when the applicant submits a PFC later than 60 days prior to the date of the PAS submission or does not submit a PFC, or when the PFC is found to be incomplete or inaccurate or the information submitted in the PFC differs significantly from the PAS submission. See page 8 of the GDUFA III commitment letter.

	90% within 10 months of submission date if preapproval inspection is required and applicant meets any limitations as described under section I(B)(4)(c) relating to submission of a PFC.
Standard and Priority Minor PAS Amendments	90% within 3 months of submission date.

GDUFA defines the *date of submission* as the date a generic drug submission (such as an ANDA, ANDA amendment, or ANDA prior approval supplement) or Type II API DMF arrives in the Electronics Submissions Gateway (ESG) of FDA.[19] If a submission arrives in physical media form in eCTD format, it is deemed to be submitted on the day it arrives at FDA's appropriate designated document room.[20] As described in the GDUFA III commitment letter, FDA will calculate the goal date from the day after a submission.[21]

Filing an unsolicited amendment[22] to a PAS may revise the existing goal date associated with that PAS. FDA will assess and act on unsolicited PAS amendments submitted during the assessment cycle by the later of the goal date for the original PAS submission/solicited amendment or the goal date assigned in accordance with the above goals for standard and priority PAS amendments FDA will assess and act on unsolicited PAS amendments submitted between assessment cycles during the next assessment cycle by the later of the goal date for the subsequent solicited amendments or the goal date assigned in accordance with the above goals for standard or priority PAS amendments.

With limited exceptions, FDA strongly recommends that, at the time of submission, a supplement should be complete and ready for a comprehensive assessment. Modifications to the supplement, in the form of an amendment, should be made only to clarify part of the already submitted supplement or to answer specific questions raised by the FDA assessment team. FDA

[19] See 21 U.S.C. 379j-42(a)(6)(A);) see also the guidance for industry *Providing Regulatory Submissions in Electronic Format – Receipt Dates* (February 2014). These submissions are deemed to be submitted to FDA on the day when transmission to the ESG is completed, except when the submission arrives on a weekend, Federal holiday, or a day when the FDA office that will assess the submission is otherwise not open for business. In that case, the submission is deemed to be submitted on the next day when that office is open for business. Additional information concerning the FDA ESG is available at http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm.

[20] 21 USC 379j-42(a)(66)(B); see also guidance for industry *Providing Regulatory Submissions in Electronic Format – Receipt Dates*,

[21] GDUFA III commitment letter at 4.

[22] A solicited amendment is an amendment submitted in response to a complete response (CR) letter. A CR letter refers to a written communication to an applicant or DMF holder from FDA, usually describing all the deficiencies the agency has identified in an ANDA (including pending amendments) or a DMF that must be satisfactorily addressed before the ANDA can be approved. CR letters reflect a complete assessment and require a complete response from industry to restart the clock. See the GDUFA III commitment letter at 45; see also § 314.110. An unsolicited amendment is an amendment with information not requested by the FDA except for those unsolicited amendments considered routine or administrative in nature that do not require scientific assessment. GDUFA III commitment letter at 48.

does not recommend that modifications expand or broaden the scope of the already submitted supplement unless the Agency requested a modification to the PAS.[23]

C. Inspections for PAS Submissions

As outlined above, the GDUFA goal date for a PAS depends on whether the PAS requires an inspection. If a PAS does not require an inspection, the goal date is either 4 or 6 months from the date of submission; but if a PAS requires an inspection, the goal date is either 8 or 10 months from the date of submission.[24] Establishments that are required to be registered under section 510 of the FD&C Act (21 U.S.C. 360) and § 207.20 of the FDA regulations (21 CFR 207.20) are subject to inspection to ensure they comply with current good manufacturing practice (CGMP) regulations.[25] Determining whether an inspection is required for a PAS is within the discretion of FDA and depends on the nature of the supplement.

Generally, we expect that any submitted PAS that requires an assessment of the need for an inspection, including, for example, a PAS involving a facility not approved in the original ANDA or involving a fundamental change in the manufacturing process or technology, will be treated initially as a PAS requiring an inspection and will be assigned an 8 or 10-month GDUFA goal date; however, the GDUFA goal date can be revised to 4 or 6 months if it is later determined that an actual inspection is not required for that PAS.[26] Conversely, an initial goal date of 6 months occasionally may change to a 10-month goal date if, during the assessment, FDA determines an inspection is necessary.

D. Submission of Supplements[27]

Any PAS to an approved ANDA should identify on the first page of the submission that it is a PAS. To facilitate processing, FDA recommends that the applicant provide the following information on the first page of the submission:

1. A statement indicating whether the PAS is for a new-strength product
2. A statement indicating whether the PAS is for a request for proprietary name assessment
3. A statement indicating whether the PAS is for a Risk Evaluation and Mitigation Strategy (REMS) or a REMS modification

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[23] See guidance for industry *ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018) for more detail on how submission of amendments may affect an application's assessment goal dates.

[24] As explained in section III.B of this guidance, filing an amendment to a PAS may revise the goal date associated with that PAS.

[25] See section 510(h) of the FD&C Act; 21 CFR parts 210-216.

[26] Under the GDUFA III commitment letter, the 8-month goal date is available to priority PASs requiring an inspection when the applicant submits a complete and accurate Pre-Submission Facility Correspondence (PFC) no later than 60 days prior to the date of the PAS submission and the PFC is found to be complete, accurate, and remain unchanged at the time of the PAS submission. See pages 7-8 of the GDUFA III commitment letter.

[27] See also FDA's draft guidance for industry, *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions* (Dec. 2021). When final, this guidance will represent the current thinking of FDA.

4. A statement indicating whether the submission is an amendment to a PAS, and if so, whether it is a major or minor amendment
5. A statement indicating whether the PAS contains any manufacturing or facilities changes
6. A list of the specific assessment disciplines to assess the PAS (Chemistry, Biopharmaceutics, Labeling, DMF, Bioequivalence, Microbiology, or Clinical)
7. If expedited assessment is requested, the label *Expedited Review Request* should be placed prominently at the top of the submission. The submission should include a basis for the expedited assessment request
8. If the submission is part of a grouped supplement (see section III.E.1 below), a statement identifying the additional submissions for the same/identical proposed change(s)" should be added. This request would greatly facilitate OPQ's identification of grouped supplements).

E. Other Matters

1. Grouped Supplements

Grouped supplements are multiple supplements submitted to ANDAs by a single applicant for the same chemistry, manufacturing, and controls (CMC) change to each application. For further information on grouped supplements, refer to the Manual of Policies and Procedures 5015.6, Rev. 1, *Review of Grouped Product Quality Supplements*, or its latest revision.

In addition to grouped supplements, there are alternative ways of submitting multiple PASs for the same change. For example, for some changes (e.g., widening of an approved specification or introduction of a new API supplier), once a PAS is submitted and approved for the lead ANDA, subsequent supplements for the same change to other ANDAs may be classified as CBE-30s. The Agency recommends that applicants contact the appropriate assessment division beforehand to ensure the change is appropriate for a PAS followed by a CBE-30, or if there are specific questions regarding this alternative.

2. Incorrect Reporting Category

If FDA finds that a supplement submitted as a CBE supplement should have been submitted as a PAS, it will notify the applicant. The applicant is not required to withdraw the CBE supplement because when FDA sends a letter explaining that the applicant's submission is not accepted as a CBE supplement, FDA administratively closes the CBE supplement, and it is considered withdrawn. The applicant may resubmit the supplement as a PAS and the GDUFA performance goals will apply to that PAS.

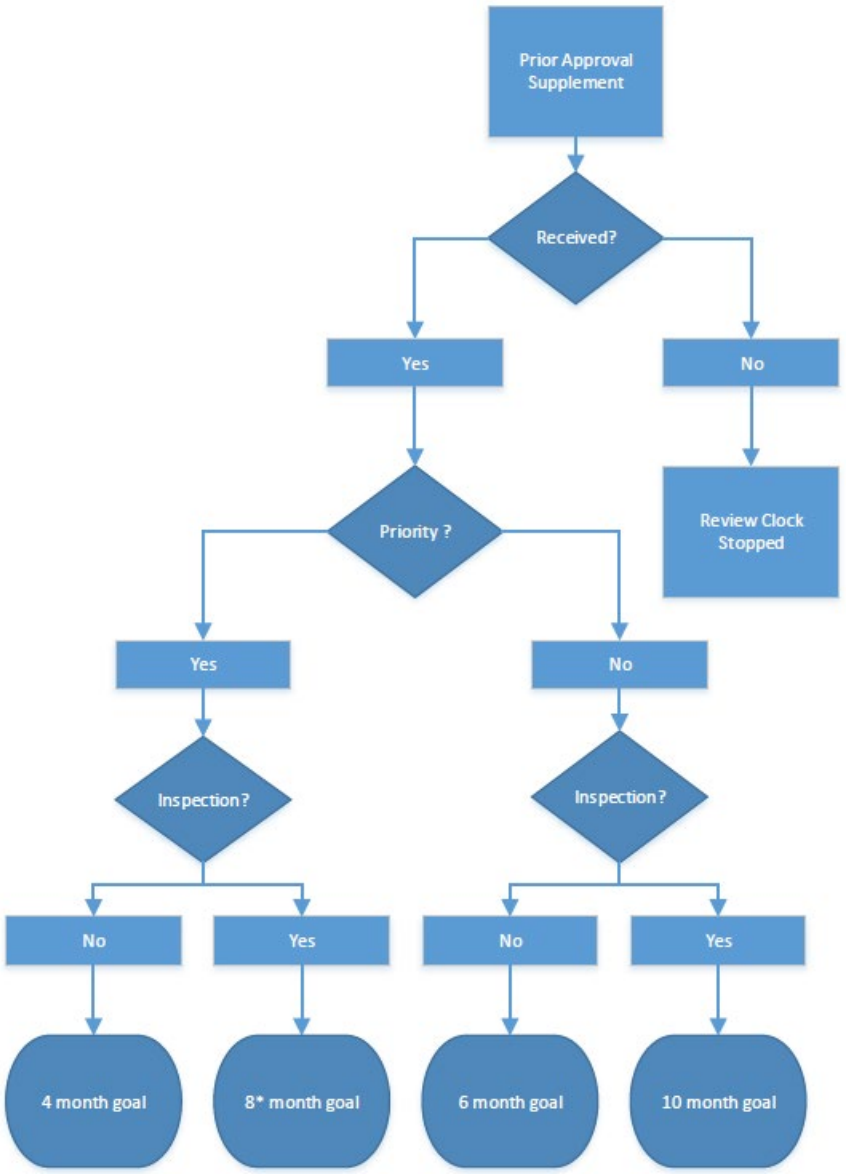
3. Reconsideration of Incorrect Reporting Category Determination

An applicant may request reconsideration of FDA's supplement reporting category determination.[28] If an applicant disagrees with the outcome of the reconsideration, the applicant may initiate a formal appeal.[29] Any applicant seeking an appeal *above* the division level should first seek reconsideration *at* the division level (21 CFR 314.103).

[28] See FDA's draft guidance for industry, Requests for Reconsideration at the Division Level Under GDUFA (Oct. 2017). When final, this guidance will represent the current thinking of FDA.

[29] The process for appeals above the division level is outlined in the guidance for industry and assessment staff *Formal Dispute Resolution: Sponsor Appeals Above the Division Level* (November 2017).

APPENDIX A – SUPPLEMENTS FLOW CHART



* Under the GDUFA III commitment letter, the 8-month goal is available to priority PASs and priority PAS major amendments when the applicant submits a complete and accurate PFC no later than 60 days prior to the date of the PAS or PAS major amendment submission and the PFC is found to be complete, accurate and remains unchanged at the time of the PAS or PAS major amendment submission. Please see the draft guidance for industry *ANDAs: Pre-Submission of Facility Information Related to Prioritized Generic Drug Applications (Pre-Submission Facility Correspondence) (October 2022)* for further information on PFC.

If an amendment is filed to the supplement, it may change the goal date. Please see the guidance for industry *ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA* for further information. In addition, the 10-month and 8-month goal dates can change to 6-month and 4-month goal dates, respectively, if an inspection is deemed unnecessary.

Similarly, 4-month and 6-month goal dates can change to 8-month and 10-month goal dates, respectively, if during the review, an inspection is ultimately deemed necessary.