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)

October 2016
Generics

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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 of 2012 (GDUFA) relates to PAS submissions. The guidance also describes the performance metric goals outlined in the GDUFA 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 GDUFA performance metric goals.

Specifically, this guidance describes how the GDUFA performance metric 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

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

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] The performance metric goals were proposed jointly by FDA and representatives of the generic drug industry. See GDUFA Program Performance Goals and Procedures for fiscal years 2015 through 2017 (Commitment Letter), available at http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf.

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

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On July 9, 2012, the President signed GDUFA into law.[4] GDUFA is designed to speed the delivery of safe and effective generic drugs to the public and reduce costs to industry.

Congress enacted GDUFA based on an agreement that FDA and representatives of the generic drug industry negotiated to address a growing number of regulatory challenges. GDUFA aims to put FDA's generic drug program on a firm financial footing and ensure timely access to safe, high-quality, affordable generic drugs. GDUFA enables FDA to assess user fees to fund critical and measurable improvements to FDA's generic drugs program and to bring greater predictability and timeliness to the review of generic drug applications.

GDUFA requires that FDA and human generic drug manufacturers meet certain requirements and commitments. In the Commitment Letter that accompanies the legislation, FDA committed to review and act on a certain percentage of PASs within a specified period from the date of submission for receipts in fiscal year (FY) 2015 through FY 2017. The percentage of PASs that FDA has committed to review and act on increases with each fiscal year; the deadlines for review also depend on whether consideration of a PAS requires an inspection.

GDUFA also establishes 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 of October 1, 2012, ANDA applicants are required to pay application fees when they submit ANDAs and PASs. Additionally, Type II active pharmaceutical ingredient (API) DMF holders are subject to a DMF fee the first time an initial letter of authorization references that DMF in an ANDA or PAS.[5] More information about these fees can be found in the following documents:

- Draft guidance for industry *Generic Drug User Fee Amendments of 2012: Questions and Answers*, Revision 1 (draft GDUFA user fee Q&A guidance)[6]

[4] Public Law 112-144, Title III.

[5] Procedures for ANDA and PAS submissions are set forth in FDA's regulations in part 314 (21 CFR part 314).

[6] In the *Federal Register* of September 10, 2013 (78 FR 55261), FDA announced the availability of the draft GDUFA user fee Q&A guidance. Several other draft guidances are referenced throughout this document. When finalized, these guidances will represent FDA's current thinking on the respective topics. For the most recent version of a guidance, check the FDA drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, or http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm.

- *Federal Register* notice, Generic Drug User Fee – Abbreviated New Drug Application, Prior Approval Supplement, Drug Master File, Final Dosage Form Facility, and Active Pharmaceutical Ingredient Facility Fee Rates for Fiscal Year 2014 (78 FR 46977, August 2, 2013).

III. IMPACT OF GDUFA PERFORMANCE METRIC GOALS ON PAS SUBMISSIONS

FDA regulations lay out requirements for making and reporting changes to approved ANDA applications (see 21 CFR 314.70). Under GDUFA and as part of FDA's commitments under GDUFA, the generic industry and FDA have agreed to certain performance metric goals, including those applicable to PASs. This section describes the specific performance metric goals that apply to PASs and amendments to PASs submitted to ANDAs under GDUFA.

Under the Commitment Letter,[7] the GDUFA performance metric goals described in this guidance apply only to holders of an ANDA who electronically submit a PAS on or after October 1, 2014.[8] The performance goals do ***not*** apply to an amendment to a PAS if the PAS was submitted before October 1, 2014, even if the amendment is submitted on or after October 1, 2014.

The GDUFA performance metric goals also 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, 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.[9] 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.

[7] Supra note 2.

[8] Per the Commitment Letter, prior approval supplements subject to the GDUFA performance metric goals must be submitted in electronic format. *Id*.

[9] 21 U.S.C. 356a.

- § 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.[10]

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 submission of the supplement to FDA at least 30 days before the distribution of the drug product made using the change.[11]
    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.[12]

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.[13]

The criteria for submitting information as a PAS, as a CBE, or in an annual report were not changed by GDUFA.[14] 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)* guidance and the *Changes to an Approved NDA or ANDA* guidance.

[10] § 314.70(b).

[11] § 314.70(c)(3).

[12] § 314.70(c)(6).

[13] § 314.70(d).

[14] 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*.

B. GDUFA Performance Metric Goals for PAS Submissions

The Commitment Letter outlines the performance metric goals FDA agreed to meet for reviewing and acting on PASs submitted in FY 2015 through FY 2017.[15] Specifically, FDA agreed to:

- Review and act on 60% of complete PASs that do not require inspection within 6 months from the date of submission for receipts in FY 2015.
- Review and act on 60% of complete PASs that require inspection within 10 months from the date of submission for receipts in FY 2015.
- Review and act on 75% of complete PASs that do not require inspection within 6 months from the date of submission for receipts in FY 2016.
- Review and act on 75% of complete PASs that require inspection within 10 months from the date of submission for receipts in FY 2016.
- Review and act on 90% of complete PASs that do not require inspection within 6 months from the date of submission for receipts in FY 2017.
- Review and act on 90% of complete PASs that require inspection within 10 months from the date of submission for receipts in FY 2017.

The Commitment Letter defines *submission date* as the date an ANDA, ANDA amendment, ANDA supplement, or Type II API DMF arrives in the Electronics Submissions Gateway (ESG) of FDA.[16] 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.[17] FDA's performance goal obligations under GDUFA start on the submission date of a PAS or amendment to a PAS. As described in the Commitment Letter, the performance goals identified in this guidance apply only to those PASs, and amendments thereto, submitted electronically to ANDAs and PASs that have been submitted electronically in or after FY 2015 (on or after October 1, 2014).[18]

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[15] Under GDUFA, action on a PAS means issuing a complete response letter, an approval letter, a tentative approval letter, or a refuse-to-receive action (Commitment Letter at 14, supra note 2). The performance metric goals appear on page 12 of the Commitment Letter.

[16] Commitment Letter at 16, supra note 2; see also the guidance for industry *Providing Regulatory Submissions in Electronic Format – Receipt Dates* (Receipt Dates guidance). 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 review 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.

[17] 21 USC 379j-42(a)(5)(B); see also the Receipt Dates guidance, supra note 16.

[18] Amendment metric goals are added to the original review goal (Commitment Letter at page 10, supra note 2). The adjustment made to the ANDA or PAS review goal assumes that the amendment is amending a submission that has been assigned a goal date (i.e., made electronically, following the eCTD format at the date of submission). If an

Because the Commitment Letter specifies the review period as a number of months "from the date of submission," FDA counts the submission date as the first day of the review period.[19] Also, per the language in the Commitment Letter, FDA calculates the goal date in months. Thus, for example, if a complete PAS that does not require an inspection is submitted on November 3, 2015, its 6-month GDUFA goal date for review and action by FDA becomes May 2, 2016. FDA will provide the applicant with notice of the GDUFA goal date. Filing an amendment to a PAS can revise the existing goal date associated with that PAS, which is discussed in more detail in section III.E of this guidance.

C. Fee-Related RTR Standards and PAS Submissions under GDUFA

FDA regulations in § 314.101 set forth the circumstances in which FDA can refuse to receive a PAS.[20] FDA's performance goal obligations under GDUFA start when a PAS is submitted to FDA, which is the day the PAS arrives in the ESG or appropriate designated document room.[21] However, if FDA refuses to receive a PAS, the GDUFA review clock stops. The applicant can submit a corrected or new supplement, but the supplement requires a new GDUFA fee,[22] starts a new GDUFA review clock, and results in a new goal date for that PAS.

GDUFA added to FDA's existing RTR standards for technical deficiencies certain conditions under which outstanding user fee obligations result in FDA refusing to receive a PAS. Under GDUFA, the following fee-related actions can result in FDA refusing to receive a PAS:

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applicant submits an original ANDA or PAS that is not in the applicable electronic format and a goal date has not been assigned, any subsequent amendment, even if it is submitted electronically, does not have a goal date associated with it that can be adjusted.

[19] FDA follows this approach in implementing provisions that specify a period "from the date of" some triggering event. *See, e.g., Mutual Pharm. Co. v. Watson Pharms., Inc.*, No. 09-5421, 2010 WL 446132 (D.N.J. Feb. 8, 2010) (noting that 7-year orphan drug exclusivity (under section 527(a) of the FD&C Act) for a drug approved on July 30, 2009, ends on July 29, 2016); Letter from FDA to C. Landmon re: Docket No. FDA-2009-N-0184, at 1-2 (Oct. 23, 2009) (5-year new chemical entity exclusivity (under section 505(j)(F)(ii) of the Act) commenced on drug approval date of Feb. 23, 2007, and expired on Feb. 22, 2012).

We note that goal dates agreed to under the Prescription Drug User Fee Act (PDUFA) are calculated differently because the PDUFA Commitment Letter does not specify review periods "from the date of" a triggering event. *See* PDFUA Commitment Letter, available at http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf.

[20] §§ 314.101(d)-(e) and 314.71(c).

[21] See supra notes 16-17.

[22] If FDA refuses to receive an ANDA or PAS for reasons other than failure to pay GDUFA fees, a refund of 75% of the application fee paid for that application or supplement will be made to the applicant (21 U.S.C. 379j-42(a)(3)(D)). The resubmission of that application or supplement is subject to a full application fee (21 U.S.C. 379j-42(a)(3)(E)).

- An applicant fails to pay the application fee within 20 calendar days of submitting the supplement[23]
- A supplement references a Type II API DMF that is not on the public *available for reference* list because of non-payment of the GDUFA DMF fee[24]
- A PAS references a facility on the facility arrears list for failure to pay the GDUFA facility fee(s)[25]
- The PAS applicant is the owner of a facility on the facility arrears list[26]
- The PAS applicant is affiliated with the owner of a facility on the facility arrears list[27]
- The PAS applicant is listed on the backlog arrears list[28]
- The PAS applicant is affiliated with an entity on the backlog arrears list[29]

In all of these cases, FDA will refuse to receive a PAS until all user fee obligations have been satisfied. If a PAS is substantially complete except for failure to pay the PAS user fee, the PAS will be deemed received as of the date the fee is paid in full. Similarly, if FDA has refused to receive the PAS because it referenced a facility on the arrears list, FDA will receive the PAS once the facility is removed from the arrears list, if the PAS is otherwise substantially complete. Upon satisfaction of all applicable user fee obligations, CDER's Office of Management issues a formal correspondence indicating the adjusted receipt date (i.e., the date on which all outstanding user fee obligations were satisfied in full) for which the PAS is eligible, assuming all other applicable requirements for receipt of a PAS have been met.[30] Adjustment of the receipt date results in a new GDUFA goal date for that PAS.

FDA can refuse to receive a PAS for other reasons unrelated to the failure to meet GDUFA fee obligations, but those other reasons are not discussed in this guidance. For more information on FDA's RTR standards, including the timing of RTR decisions, refer to § 314.101 of FDA's regulations, as well as related FDA guidances for industry.[31]

D. Inspections for PAS Submissions

[23] 21 U.S.C. 379j-42(g)(3).

[24] 21 U.S.C. 379j-42(g)(2).

[25] 21 U.S.C. 379j-42(g)(4)(A).

[26] 21 U.S.C. 379j-42(g)(4)(A)(i).

[27] 21 U.S.C. 379j-42(g)(4)(A)(i).

[28] 21 U.S.C. 379j-42(g)(1).

[29] 21 U.S.C. 379j-42(g)(1).

[30] 21 CFR 314.101(d)-(e) and 314.71(c).

[31] Related FDA guidances include, but are not limited to, the guidance for industry *ANDA Submissions — Refuse-to-Receive Standards* and the draft GDUFA user fee Q&A guidance, supra note 6.

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 6 months from the date of submission; but if a PAS requires an inspection, the goal date is 10 months from the date of submission.[32]

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.[33] 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 a 10-month GDUFA goal date; however, the GDUFA goal date can be revised to 6 months if it is later determined that an actual inspection is not required for that PAS. Although not typical, an initial goal date of 6 months occasionally may change to a 10-month goal date if, during the review, FDA determines an inspection is necessary.

E. Amendments to PAS Submissions

As noted above, if an amendment is made to a PAS, the GDUFA goal date associated with that PAS may be revised. With limited exceptions, FDA strongly recommends that, at the time of submission, a supplement should be complete and ready for a comprehensive review. 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 review team. FDA does not recommend that modifications expand or broaden the scope of the already submitted supplement unless the Agency requested them—there may be circumstances in which an amendment must be made to a PAS.

The Commitment Letter outlines FDA's GDUFA performance metric goals for amendments. They are grouped as Tier 1, Tier 2, or Tier 3.[34]

- Tier 1

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

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

[34] For more detail on how FDA intends to classify major amendments, minor amendments, and easily correctable deficiencies to original ANDAs and to PASs submitted after October 1, 2014, under GDUFA, see the draft guidance for industry *ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA* (Amendments Guidance). Once finalized, that guidance will represent FDA's current thinking on the tier system and easily correctable deficiencies.

Tier 1 amendments include the first solicited major amendment, the first five minor amendments, and all delaying amendments.[35] Delaying amendments address actions by a third party that would cause delay or impede application review or approval timing and that were not, or might not have been initially recognized by FDA as, necessary when the application was submitted.[36]

- Tier 2

Tier 2 amendments include all unsolicited amendments not arising from delaying actions as determined by FDA, taking into account the facts and information supplied by the ANDA applicant, excepting those amendments that only remove information from review.

The GDUFA performance metric goals for Tier 1 and Tier 2 amendments vary from 3 months to 12 months, depending on the type of amendment filed.[37]

- Tier 3

Tier 3 amendments include any solicited major amendment subsequent to the first major amendment, and any solicited minor amendment subsequent to the fifth minor amendment. There are no GDUFA performance metric goals for Tier 3 amendments.[38]

As explained in the Commitment Letter, all amendment metric goals are incremental, and the periods specified are calculated from the date of submission. Thus, the performance metric goal for an amendment to a PAS will be added to the original goal date for that PAS.

The Commitment Letter explains in more detail the performance metric goals for each amendment tier; this information is not repeated here. However, the following are some examples of how an amendment to a PAS can have an impact on the GDUFA goal date for that PAS. If an amendment to a PAS is submitted after the issuance of a complete response (CR) letter, this sets a new goal date for the PAS. For example:

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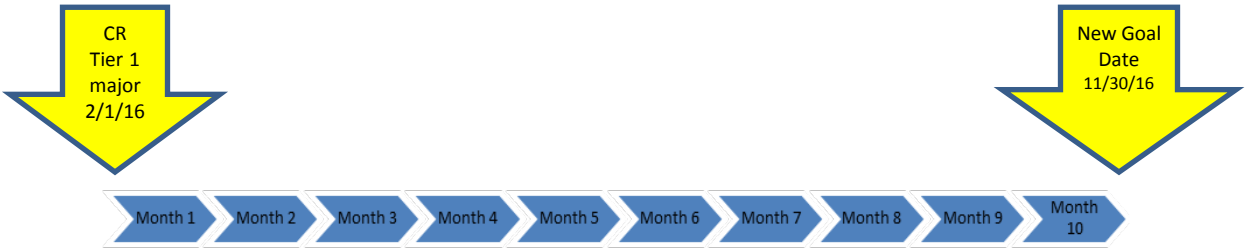
[35] A solicited amendment is an amendment submitted in response to a complete response (CR) letter. A CR letter refers to a written communication to an applicant or DMF holder from FDA, usually describing all the deficiencies the agency has identified in an ANDA (including pending amendments) or a DMF that must be satisfactorily addressed before the ANDA can be approved. CR letters reflect a complete review and require a complete response from industry to restart the clock. See Commitment Letter at 14, supra note 2; see also § 314.110. An unsolicited amendment is an amendment with information not requested by the FDA except for those unsolicited amendments that are considered routine or administrative in nature and that do not require scientific review. Commitment Letter at 16-17, supra note 2.

[36] Commitment Letter at 14, supra note 2.

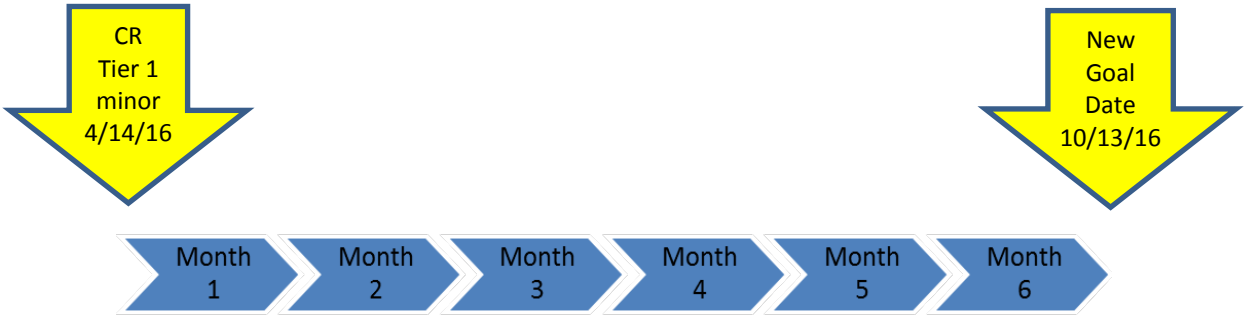
[37] See the Amendments Guidance, supra note 34, for a more thorough description and examples of performance metric goals for Tier 1 and Tier 2 amendments.

[38] Id. at 10-11.

- If a Tier 1 major amendment with a 10-month metric is submitted on February 1, 2016, in response to a CR letter for a PAS, this establishes a new GDUFA goal date of 10 months from the date of submission of the major amendment for that PAS. The new goal date is November 30, 2016.



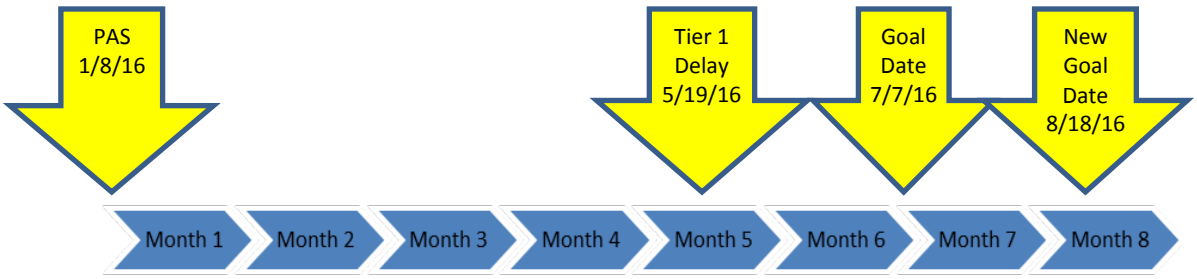
- If a Tier 1 minor amendment with a 6-month metric is submitted on April 14, 2016, in response to a CR letter for a PAS, this establishes a new GDUFA goal date of 6 months from the date of submission of the minor amendment for that PAS. The new goal date is October 13, 2016.



Any subsequent amendments submitted to a PAS after the issuance of a CR letter can also adjust the goal date for the PAS and can add time to the review clock.

If an amendment to a PAS is submitted before the issuance of a CR letter, this can adjust the goal date for the original PAS. For example:

- A PAS with a 6-month metric is submitted on January 8, 2016, and given a goal date of July 7, 2016. A Tier 1 delaying amendment with a 3-month metric is submitted in month 5 of the original review cycle on May 19, 2016. Submission of the amendment adjusts the GDUFA review clock and extends the goal date 3 months from May 19, 2016, the date of submission of the amendment for that PAS. The new goal date is August 18, 2016.



Any subsequent amendments to a pending PAS that are submitted before the issuance of a CR letter can also adjust the goal date for the PAS and can add time to the review clock.

Administrative amendments are routine in nature and do not require scientific review.[39] Administrative amendments do not affect the goal dates for the application and, as a result, are considered neither Tier 1, Tier 2, nor Tier 3 amendments.

F. Submission of Supplements

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 submission is an amendment to a PAS, and if so the corresponding tier classification
4. A statement indicating whether the PAS contains any manufacturing or facilities changes
5. A list of the specific review disciplines to review the PAS (Chemistry, Labeling, DMF, Bioequivalence, Microbiology, or Clinical)
6. If expedited review 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 review request.

G. 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, *Review of the Same Supplemental Change to More than One NDA or ANDA in More Than One Review Division*, or its latest revision.

[39] For more detail on administrative amendments, see the Amendments Guidance, supra note 34.

Although the submissions are considered a group, each supplement in the group is considered its own individual submission and therefore would require a GDUFA PAS fee for each ANDA identified in the group.[40] Thus, for example, if a group PAS change is submitted to 10 ANDAs, then 10 GDUFA PAS fees should be remitted. Because the grouped supplements are being reviewed together, generally they will have the same GDUFA goal date.

If the applicant identifies a lead ANDA for a group of PASs and only one fee is paid (or fewer than all the fees for the group are paid), the lead supplement and any supplements with the requisite paid fee can be received, but any other supplements without the requisite paid fee cannot be received. If the other fee-deficient supplements are then submitted at a later date, this can result in different GDUFA goal dates for the supplements initially received and the subsequently filed supplements.

There are alternatives to 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 review 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.

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 for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls.*

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 for FDA approval before distribution of the drug product, along with the required GDUFA user fee.[41] The GDUFA performance metric goals and applicable user fees will apply to that PAS.[42] As explained in section III.B, the GDUFA review clock will start from the date of submission of that PAS. For example:

- An applicant submits a CBE supplement on November 17, 2015. FDA determines that the applicant should have submitted the supplement as a PAS and notifies the applicant that the proposed change was submitted incorrectly as a CBE supplement. Upon issuance

[40] 21 USC 379j-42(a)(3) (a PAS is subject to a fee "for each such submission").

[41] § 314.70(c)(5)(i).

[42] Draft GDUFA user fee Q&A guidance at 13, supra note 6.

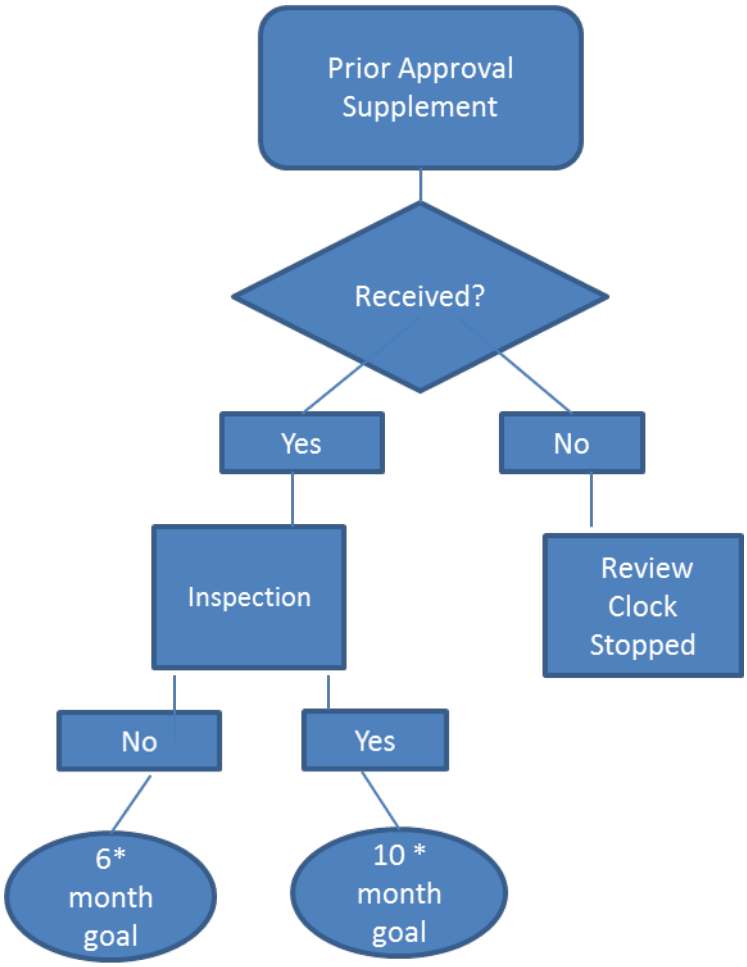
of the letter explaining that the applicant's submission is not accepted as a CBE supplement, FDA considers the CBE withdrawn. On December 1, 2015, the applicant resubmits the supplement as a PAS that meets all the submission requirements, including payment of the applicable GDUFA user fee. The GDUFA review clock commences on December 1, 2015.

3. Reconsideration of Incorrect Reporting Category Determination

An applicant may request reconsideration of FDA's supplement reporting category determination. These requests will be reviewed and managed on a case-by-case basis. If an applicant is requesting reconsideration of a supplement reporting category, the applicant must submit a written request for reconsideration within 10 business days of FDA's notice to the applicant that the applicant's submission was not accepted as a CBE supplement. If an applicant disagrees with the outcome of the reconsideration, the applicant may initiate a formal appeal.[43] Any applicant seeking an appeal *above* the division level should first seek reconsideration *at* the division level (21 CFR 314.103).

[43] The process for appeals above the division level is outlined in the draft guidance for industry *Formal Dispute Resolution: Appeals Above the Division Level*. Once finalized, that guidance will represent FDA's current thinking on the issue.

APPENDIX A – GDUFA SUPPLEMENTS FLOW CHART



* If an amendment is filed to the supplement, it may change the goal date. See draft guidance for industry *ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA*, flow chart at Appendix A. In addition, the 10-month goal date can change to a 6-month goal date if an inspection is deemed unnecessary, and a 6-month goal date can change to a 10-month goal date if, during the review, an inspection is deemed necessary.