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 2017
Generics

Revision 1

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Contains Nonbinding Recommendations

Guidance for Industry[1]
ANDA Submissions – Prior Approval Supplements Under GDUFA

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 Program Performance Goals and Procedures for fiscal years 2015 through 2017 (GDUFA I) and the GDUFA Reauthorization Performance Goals and Program Enhancements fiscal years 2018-2022 (GDUFA II) Commitment Letters 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

[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 the GDUFA I Commitment Letter, available at http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf and the GDUFA II Commitment Letter, available at https://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm525234.pdf.

[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 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 the generic drug industry meet certain requirements and commitments. In the GDUFA I Commitment Letter that accompanied 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. In accordance with the GDUFA II Commitment Letter, FDA reauthorized its GDUFA I obligations. The percentage of PASs that FDA has committed to review and act on increases with each fiscal year, peaking in FY 2017; the deadlines for review also depend on whether consideration of a PAS requires an inspection.

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.[5]

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 drug industry and FDA have agreed to certain performance metric goals,

[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).

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.

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.[6] 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.[7]

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

[6] 21 U.S.C. 356a.

[7] § 314.70(b).

submission of the supplement to FDA at least 30 days before the distribution of the drug product made using the change.[8]

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.[9]

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.[10]

The criteria for submitting information as a PAS, as a CBE, or in an annual report were not changed by GDUFA.[11] 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.

B. GDUFA Performance Metric Goals for PAS Submissions

The GDUFA I Commitment Letter outlines the performance metric goals FDA agreed to meet for reviewing and acting on PASs submitted in FY 2015 through FY 2017.[12] 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.

[8] § 314.70(c)(3).

[9] § 314.70(c)(6).

[10] § 314.70(d).

[11] 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*.

[12] 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 (GDUFA I Commitment Letter at 14, supra note 2). The performance metric goals appear on page 12 of the GDUFA I Commitment Letter.

- 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 GDUFA II Commitment Letter outlines the performance metric goals FDA agreed to meet for reviewing and acting on PASs submitted in FY 2018 through FY 2022[13] and delineates between standard and priority PASs for performance metrics purposes.[14] It further revises FDA's GDUFA performance metric goals for amendments, eliminating the Tier system.[15] Specifically, FDA agreed to the goals outlined as follows:

Submission Type	Performance Goal
Standard PASs or PAS Major Amendments	90% reviewed within 6 months if preapproval inspection not required
	90% reviewed within 10 months if preapproval inspection required
Priority PASs or PAS Major Amendments	90% reviewed within 4 months if preapproval inspection not required
	90% reviewed within 8 months if preapproval inspection required and applicant submits a complete and accurate Pre-Submission Facility Correspondence (PFC) no later than 60 days prior to the date of the PAS or amendment submission, which remains unchanged[16]
	90% reviewed within 10 months if preapproval inspection is required and applicant fails to submit a complete and accurate PFC no later than 60 days prior to the date of the PAS or amendment submission, or information in a complete and accurate submitted PFC changes
Standard and Priority PAS Minor Amendments	90% reviewed within 3 months of submission date

[13] The performance metric goals appear on pages 6-8 of the GDUFA II Commitment Letter.

[14] The GDUFA II Commitment Letter defines "priority" as "submissions affirmatively identified as eligible for expedited review pursuant to CDER's Manual of Policy and Procedures (MAPP) 5240.3, *Prioritization of the Review of Original ANDAs, Amendments and Supplements*, as revised. See page 27 of the GDUFA II Commitment Letter.

[15] For more detail on how FDA intends to classify major and minor amendments to original ANDAs and PASs under GDUFA, see the draft guidance for industry *ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA* (Amendments Guidance). Once finalized, that guidance will represent FDA's current thinking on the classification and categories of amendments.

[16] In accordance with the GDUFA II Commitment Letter, FDA will review and act on 90% of priority PASs and PAS major amendments within 8 months of submission when a preapproval inspection is required if the applicant submits a 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.

The GDUFA II Commitment Letter provides a timeline for the submission of PFCs, i.e., 2 months prior to the PAS submission. The FDA Reauthorization Act of 2017 at section 801 requires submission of PFCs no later than 60 days prior to the submission of the original ANDA. To ensure that PFCs for PASs and major amendments to PASs are submitted consistent with PFCs for original submissions, FDA has inserted the timing required in the FDA Reauthorization Act. See the GDUFA II Commitment Letter at pages 6-7, 26. For more detail on the submission of PFCs, see the draft guidance for industry *ANDAs: Pre-Submission Facility Correspondence Associated with Priority Submissions.*

The GDUFA I 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.[17] 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.[18] FDA's performance goal obligations under GDUFA start on the submission date of a PAS or amendment to a PAS. As described in the GDUFA I 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). [19]

Consistent with GDUFA I, FDA counts the submission date as the first day of the review period.[20] Also, per the language in the GDUFA I Commitment Letter, FDA calculates the goal date in months. Thus, for example, if a complete standard PAS that does not require an inspection is submitted on November 3, 2018, its 6-month GDUFA goal date for review and action by FDA becomes May 2, 2019. FDA will provide the applicant with notice of the GDUFA goal date.

Filing an unsolicited amendment[21] to a PAS may revise the existing goal date associated with that PAS. FDA will review and act on unsolicited PAS amendments submitted during the

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[17] GDUFA I 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.

[18] 21 USC 379j-42(a)(5)(B); see also the Receipt Dates guidance, supra note 19.

[19] Amendment metric goals are added to the original review goal (GDUFA I 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 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.

[20] 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 FD&C 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. *See* the PDUFA Commitment Letter, available at http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf.

[21] 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 the GDUFA I Commitment Letter at 14, supra note 2; see also § 314.110. An

review cycle by the later of the goal date for the original submission/solicited amendment or the goal date assigned in accordance with the above goals for standard and priority review PASs. FDA will review and act on unsolicited PAS amendments submitted between review cycles 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 PASs.

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.[22]

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.[23] 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.[24] 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. 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.

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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. GDUFA I Commitment Letter at 16-17, supra note 2.

[22] See the Amendments Guidance for more detail on how submission of amendments may affect an application's review goal dates.

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

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

D. 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 PAS is for a request for proprietary name review.
3. A statement indicating whether the PAS is for a Risk Evaluation and Mitigation Strategy (REMS) or a REMS modification.
4. A statement indicating whether the submission is an amendment to a PAS, and 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 review disciplines to review the PAS (Chemistry, Biopharmaceutics, Labeling, DMF, Bioequivalence, Microbiology, or Clinical)
7. 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.

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 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: Chemistry, Manufacturing, and Controls Information.*

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 metric goals will apply to that PAS. As explained in section III.B, the GDUFA review clock will start from the date of submission of that PAS. For example:

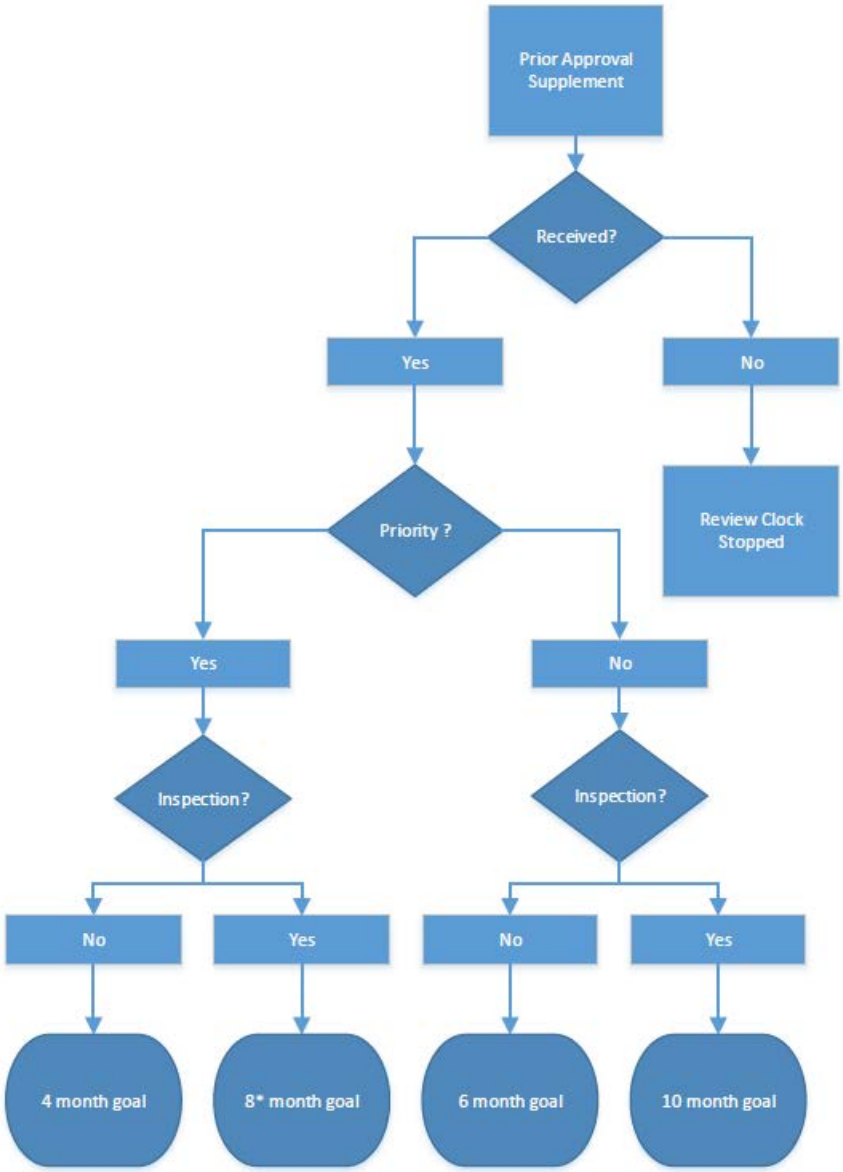
- An applicant submits a CBE supplement on November 17, 2017. FDA determines that the applicant should have submitted the supplement as a PAS and notifies the applicant that the proposed change was submitted incorrectly as a CBE supplement. Upon issuance of the letter explaining that the applicant's submission is not accepted as a CBE supplement, FDA considers the CBE withdrawn. On December 1, 2017, the applicant resubmits the supplement as a PAS that meets all the submission requirements. The GDUFA review clock commences on December 1, 2017.

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.[25] Any applicant seeking an appeal *above* the division level should first seek reconsideration *at* the division level (21 CFR 314.103).

[25] 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 II SUPPLEMENTS FLOW CHART



* 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.

If an amendment is filed to the supplement, it may change the goal date. Please see the draft 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, 6-month and 8-month goal dates can change to 8-month and 10-month goal dates, respectively, if during the review, an inspection is ultimately deemed necessary.