
Guidance for Industry ANDA Submissions — Prior Approval Supplements Under GDUFA

DRAFT GUIDANCE

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

**July 2014
Generics**

Guidance for Industry ANDA Submissions — Prior Approval Supplements Under GDUFA

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1 **Guidance for Industry¹**
2 **ANDA Submissions — Prior Approval Supplements**
3 **Under GDUFA**
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7 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
8 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
9 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
10 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
11 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
12 the appropriate number listed on the title page of this guidance.
13

14
15 **I. INTRODUCTION**
16

17 This guidance is intended to assist applicants preparing to submit to the Food and Drug
18 Administration (FDA) prior approval supplements (PASs) and amendments to PASs for
19 abbreviated new drug applications (ANDAs) submitted under section 505(j) of the Federal Food,
20 Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(j)). The guidance explains how the
21 Generic Drug User Fee Amendments of 2012 (GDUFA) relates to PAS submissions. The
22 guidance also describes performance metric goals outlined in the GDUFA Commitment Letter,
23 which FDA has agreed to meet,² and clarifies how FDA will handle a PAS and amendments to a
24 PAS for an ANDA subject to the GDUFA performance metric goals.
25

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

- 27 • A PAS subject to the refuse-to-receive (RTR) standards
- 28 • A PAS that requires an inspection³
- 29 • A PAS for which an inspection is not required
- 30 • An amendment to a PAS
- 31 • Other PAS-related matters
32

33 FDA's guidance documents, including this guidance, do not establish legally enforceable
34 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
35 be viewed only as recommendations, unless specific regulatory or statutory requirements are

¹ This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) in cooperation with the Center for Biologics Evaluation and Research (CBER).

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.

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36 cited. The use of the word *should* in Agency guidances means that something is suggested or
37 recommended, but not required.

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40 **II. BACKGROUND**

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

44

45 GDUFA is based on an agreement negotiated by FDA and representatives of the generic drug
46 industry to address a growing number of regulatory challenges. GDUFA aims to put FDA's
47 generic drug program on a firm financial footing and ensure timely access to safe, high-quality,
48 low-cost generic drugs. GDUFA enables FDA to assess user fees to fund critical and measurable
49 improvements to FDA's generic drugs program and to bring greater predictability and timeliness
50 to the review of generic drug applications.

51

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

58

59 GDUFA also establishes application fees (for ANDAs, PASs to ANDAs, and drug master files
60 (DMFs)), annual facility fees, and a one-time fee for ANDAs that were pending on October 1,
61 2012 (referred to as *backlog applications*). Beginning on October 1, 2012, ANDA applicants
62 and DMF holders are required to pay application fees when they submit ANDAs and PASs, or
63 the first time a DMF is referenced by an initial letter of authorization in an ANDA or PAS.⁵
64 More information about these fees can be found in the following documents:

65

- 66 • Draft guidance for industry on *Generic Drug User Fee Amendments of 2012: Questions*
67 *and Answers*, Revision 1 (draft GDUFA user fee Q&A guidance)⁶
- 68 • *Federal Register* notice, Generic Drug User Fee — Abbreviated New Drug Application,
69 Prior Approval Supplement, Drug Master File, Final Dosage Form Facility, and Active
70

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>.

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71 Pharmaceutical Ingredient Facility Fee Rates for Fiscal Year 2014 (78 FR 46977, August
72 2, 2013).

73 74 75 III. IMPACT OF GDUFA PERFORMANCE METRIC GOALS ON PAS 76 SUBMISSIONS 77

78 FDA regulations provide requirements for making and reporting changes to approved ANDA
79 applications as well as for making changes and submitting supplements and amendments to
80 supplements before FDA has approved the ANDA. Under GDUFA and as part of FDA's
81 commitments under GDUFA, the generic industry and FDA have agreed to certain performance
82 metric goals. This section describes the specific performance metric goals for prior approval
83 supplements (PAS) and amendments to PASs submitted to ANDAs under GDUFA.
84

85 Under the Commitment Letter,⁷ the GDUFA performance metric goals described in this
86 guidance apply only to holders of an ANDA that submit a PAS on or after October 1, 2014.⁸
87 The performance goals do *not* apply to an amendment to a PAS if the PAS was submitted before
88 October 1, 2014, even if the amendment is submitted on or after October 1, 2014.
89

90 The GDUFA performance metric goals also do not apply to new drug applications (NDAs) or
91 biologics license applications (BLAs). Nor do they apply to supplements filed for NDAs or
92 BLAs, changes-being-effected supplements, or annual report filings to NDAs, BLAs, or ANDAs.
93 In this guidance, any reference to a PAS refers only to a PAS filed for an ANDA, unless
94 otherwise clearly indicated.
95

96 A. Changes to an Approved Application 97

98 Section 506A of the FD&C Act (which was added by section 116 of the Food and Drug
99 Administration Modernization Act of 1997 (FDAMA)) provides requirements for making and
100 reporting manufacturing changes to an approved application and for distributing a drug product
101 made with such changes.⁹ The following sections of FDA's regulations set forth the
102 requirements for supplements and other changes to approved applications under section 506A:
103

- 104 • Section 314.70 describes the different reporting categories for changes to an approved
105 application.
- 106 • Section 314.71 outlines the procedures for submission of a supplement to an approved
107 application.
- 108 • Section 314.97 provides that supplements and other changes to an approved ANDA must
109 comply with the requirements of §§ 314.70 and 314.71.

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.

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Specifically, section 506A of the FD&C Act and § 314.70 of FDA regulations provide for the following reporting categories for 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 upon 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 Effectuated 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 Effectuated (CBE-0 supplement)** - A CBE-0 supplement involves certain moderate changes for which distribution can occur when 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. 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, please refer to § 314.70, as well as related guidance, including, but not limited to, the *Scale-Up and Post-approval Changes (SUPAC)* guidances and the *Changes to an Approved NDA or ANDA* guidance.¹⁴

¹⁰ § 314.70(b).

¹¹ § 314.70(c)(3).

¹² § 314.70(c)(6).

¹³ § 314.70(d).

¹⁴ These guidances and other applicable guidances are available at the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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146 **B. GDUFA Performance Metric Goals for PAS Submissions**

147

148 The Commitment Letter outlines the performance metric goals FDA agreed to meet for
149 reviewing and acting on PASs submitted in FY 2015 through FY 2017.¹⁵ Specifically, FDA
150 agreed to:

151

152 • Review and act on 60% of complete PASs that do not require inspection within 6 months
153 from the date of submission for receipts in FY 2015.

154 • Review and act on 60% of complete PASs that require inspection within 10 months from
155 the date of submission for receipts in FY 2015.

156 • Review and act on 75% of complete PASs that do not require inspection within 6 months
157 from the date of submission for receipts in FY 2016.

158 • Review and act on 75% of complete PASs that require inspection within 10 months from
159 the date of submission for receipts in FY 2016.

160 • Review and act on 90% of complete PASs that do not require inspection within 6 months
161 from the date of submission for receipts in FY 2017.

162 • Review and act on 90% of complete PASs that require inspection within 10 months from
163 the date of submission for receipts in FY 2017.

164

165 The Commitment Letter defines *submission date* as the date an ANDA, ANDA amendment,
166 ANDA supplement, or Type II active pharmaceutical ingredient (API) DMF arrives in the
167 appropriate electronic portal of FDA.¹⁶ Because the Commitment Letter specifies the review
168 period as a number of months “from the date of submission,” FDA counts the submission date as
169 the first day of the review period.¹⁷ Also, per the language in the Commitment Letter, FDA will
170 calculate the goal date in months. Thus, for example, if a complete PAS that does not require an
171 inspection is submitted on November 3, 2014, its 6-month GDUFA goal date for review and
172 action by FDA is May 2, 2015. FDA will provide the applicant with notice of the GDUFA goal

¹⁵ Under GDUFA, action on a PAS means issuing a complete response (CR) letter, an approval letter, a tentative approval letter, or a refuse-to-approve 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.

¹⁷ FDA follows this approach in implementing provisions that specify a period of time “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 7-year orphan drug exclusivity (under section 527(a) of the FD&C Act) for 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* PDUFA Commitment Letter, available at <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>.

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173 date. Filing an amendment to a PAS can revise the goal date associated with that PAS, which we
174 discuss in more detail in section III.E of this guidance.

175 C. Refuse-to-Receive Standards and PAS Submissions Under GDUFA

176
177
178 FDA regulations in § 314.101 set forth the circumstances in which FDA can refuse to receive a
179 PAS.¹⁸ FDA's performance goal obligations under GDUFA start when a PAS is submitted to
180 FDA, which is the day the PAS arrives in the electronic submission gateway.¹⁹ However, if
181 FDA refuses to receive a PAS, the GDUFA review clock stops. The applicant can submit a
182 corrected or new supplement, but the supplement requires a new GDUFA fee,²⁰ starts a new
183 GDUFA review clock, and results in a new goal date for that PAS.

184
185 GDUFA added to FDA's existing refuse-to-receive standards certain conditions under which
186 outstanding user fee obligations result in FDA refusing to receive a PAS. Under GDUFA, the
187 following fee-related actions can result in FDA refusing to receive a PAS:

- 188
189 • If an applicant fails to pay the application fee within 20 calendar days of submitting the
190 supplement²¹
- 191 • If a supplement references a Type II API DMF that is not on the public available for
192 reference list because of non-payment of the GDUFA DMF fee²²
- 193 • If a PAS references a facility on the facility arrears list for failure to pay the GDUFA
194 facility fee(s)²³
- 195 • If the PAS applicant is the owner of a facility on the facility arrears list²⁴

¹⁸ §§ 314.101(d)-(e) and 314.71(c).

¹⁹ For more information on regulatory submissions and receipt dates, see the guidance for industry *Providing Regulatory Submissions in Electronic Format — Receipt Dates* (receipt dates guidance), available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072385.pdf>. These submissions are deemed to be submitted to FDA on the day that transmission to the electronic submission gateway 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 those cases, the submission is deemed to be submitted on the next day that office is open for business. Receipt dates guidance at 3; see also Commitment Letter at 16, *supra* note 2.

²⁰ 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)).

²¹ 21 U.S.C. 379j-42(g)(3).

²² *Id.* 379j-42(g)(2). FDA will also refuse to receive a PAS that references a DMF that is otherwise unavailable for reference because it failed to pass the initial completeness assessment. See the draft guidance for industry *Initial Completeness Assessments for Type II API DMFs Under GDUFA*, available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm321884.pdf>.

²³ 21 U.S.C. 379j-42(g)(4)(A).

²⁴ *Id.* 379j-42(g)(4)(A)(i).

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- 196 • If the PAS applicant is affiliated with the owner of a facility on the facility arrears list²⁵
- 197 • If the PAS applicant is listed on the backlog arrears list²⁶
- 198 • If the PAS applicant is affiliated with an entity on the backlog arrears list²⁷

199 In all of these cases, FDA will refuse to receive a PAS until all user fee obligations have been
200 satisfied. If a PAS is substantially complete except for failure to pay the PAS user fee, the PAS
201 will be deemed received as of the date the fee is paid in full. Similarly, if FDA has refused to
202 receive the PAS because it referenced a facility on the arrears list, FDA will receive the PAS
203 once the facility is removed from the arrears list, if the PAS is otherwise substantially complete.
204 Upon satisfaction of all applicable user fee obligations, CDER's Office of Management issues a
205 formal correspondence indicating the adjusted receipt date (i.e., the date on which all outstanding
206 user fee obligations were satisfied in full) for which the PAS is eligible, assuming all other
207 applicable requirements for receipt of a PAS have been met.²⁸ Adjustment of the receipt date
208 results in a new GDUFA goal date for that PAS.
209

210 FDA can refuse to receive a PAS for other reasons unrelated to the failure to meet GDUFA fee
211 obligations, but those other reasons are not discussed in this guidance. For more information on
212 FDA's refuse-to-receive standards, please refer to § 314.101 of FDA's regulations, as well as
213 related FDA guidance for industry.²⁹
214

D. Inspections for PAS Submissions

215
216
217 As outlined above, the GDUFA goal date for a PAS depends on whether the PAS requires an
218 inspection. If a PAS does not require an inspection, the goal date is 6 months from the date of
219 submission; but, if a PAS requires an inspection, the goal date is 10 months from the date of
220 submission.³⁰
221

222 Establishments that are required to be registered under section 510 of the FD&C Act (21 U.S.C.
223 360) and § 207.20 of the FDA regulations (21 CFR 207.20) are subject to inspection to ensure
224 that they comply with current good manufacturing practice (CGMP) regulations.³¹ Determining
225 whether an inspection is required for a PAS is within the discretion of FDA and depends on the
226 nature of the supplement. In certain cases, upon submission of the PAS, it will be clear whether
227 the PAS requires an inspection for determining the GDUFA goal date for that PAS.

²⁵ Id.

²⁶ Id. 379j-42(g)(1).

²⁷ Id.

²⁸ 21 CFR §§ 314.101(d)-(e) and 314.71(c).

²⁹ Related FDA guidances include, but are not limited to, the draft guidance on *ANDA Submissions — Refuse-to-Receive Standards* and the draft GDUFA user fee Q&A guidance, *supra* note 6.

³⁰ As explained in section III.E of this guidance, filing an amendment to a PAS can revise the goal date associated with that PAS.

³¹ See section 510(h) of the FD&C Act; 21 CFR parts 210-216.

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228
229 In other cases, it is not always immediately evident upon submission whether a PAS requires an
230 inspection. Generally, we expect that any PAS that is submitted that requires an assessment of
231 the need for an inspection, including, for example, a PAS involving a facility not approved in the
232 original ANDA or involving a fundamental change in the manufacturing process or technology,
233 will be treated initially as a PAS requiring an inspection and will be assigned a 10-month
234 GDUFA goal date — the GDUFA goal date can be revised to 6 months if it is later determined
235 that an actual inspection is not required for that PAS. Although not typical, there may be the
236 occasional circumstance in which an initial goal date of 6 months may change to a 10-month
237 goal date if, during the review, FDA determines an inspection is necessary. FDA will provide
238 notice to the applicant if such a change occurs.

239
240 FDA prioritizes inspections using its risk-based approach.³² FDA prioritizes inspections of
241 establishments associated with a PAS that are otherwise approvable or eligible for tentative
242 approval except for an outstanding inspection. FDA also prioritizes inspections for
243 establishments associated with a PAS if the establishments have not been inspected previously.³³
244

245 As described in the Commitment Letter, FDA generally, among other considerations, will rely on
246 a previous inspection of a finished product site if it occurred within 2 years of the current CGMP
247 evaluation for a pending application, 3 years for an API site or a control testing laboratory, and 4
248 years for a packaging-only site. There are exceptions to this general practice, which are usually
249 related to the nature of the drug being processed or the complexity of the associated processing
250 operations. FDA intends to continue the practice of using a risk-based assessment in
251 determining the need for an inspection, guided by a 2-year cycle for finished dosage product sites
252 and a 3-year cycle for API sites and consideration of the type of finished product or API in the
253 application. Practically, this means that in making decisions about pending supplemental
254 applications for which FDA does not have current inspection information within the time period
255 indicated, FDA may use previous FDA inspection information and/or use inspection information
256 from another regulatory authority as appropriate. If FDA determines that an actual inspection is
257 not required, the goal date would be revised from 10 months to 6 months.

E. Amendments to PAS Submissions

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261 As noted above, if an amendment is made to a PAS, the GDUFA goal date associated with that
262 PAS may be revised. Generally, FDA recommends that, at the time of submission, a supplement
263 should be complete and ready for a comprehensive review. Modifications of the supplement, in
264 the form of an amendment, should be made only to clarify part of the already submitted
265 supplement or to answer specific questions raised by the FDA review team. FDA does not

³² See section 510(h)(3) of the FD&C Act; see generally *Pharmaceutical CGMPs For The 21st Century – A Risk-Based Approach*, Final Report, Sept. 2004, available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMPforDrugs/UCM176374.pdf>. See also Commitment Letter at 3-4, *supra* note 2.

³³ See Commitment Letter at 3-4, *supra* note 2.

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266 recommend that modifications expand or broaden the scope of the already submitted supplement
267 unless they are requested by FDA — there may be circumstances in which an amendment must
268 be made to a PAS.

269
270 The Commitment Letter outlines FDA’s GDUFA performance metric goals for amendments.
271 They are grouped as Tier 1, Tier 2, or Tier 3.³⁴

272
273 • Tier 1

274
275 Tier 1 amendments include the first solicited major amendment and the first five minor
276 amendments and all delaying amendments.³⁵ Delaying amendments address actions by a
277 third party that would cause delay or impede application review or approval timing and that
278 were not or might not have been initially recognized by FDA as necessary when the
279 application was submitted.³⁶

280
281 • Tier 2

282
283 Tier 2 amendments include all unsolicited amendments not arising from delaying actions as
284 determined by FDA, taking into account the facts and information supplied by the ANDA
285 applicant excepting those amendments that only remove information for review.

286
287 The GDUFA performance metric goals for Tier 1 and Tier 2 amendments vary from 3 months to
288 12 months, depending on the type of amendment filed.

289
290 • Tier 3

291
292 Tier 3 amendments include any solicited major amendment subsequent to the first major
293 amendment, and any solicited minor amendment subsequent to the fifth minor amendment.
294 There are no GDUFA performance metric goals for Tier 3 amendments.³⁷

295

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*. Once finalized, that guidance will represent FDA’s thinking on the Tier system and easily correctable deficiencies.

³⁵ A solicited amendment is an amendment submitted in response to a complete response letter. A complete response (CR) letter refers to a written communication to an applicant or DMF holder from FDA usually describing all of the deficiencies that the agency has identified in an abbreviated application (including pending amendments) or a DMF that must be satisfactorily addressed before the ANDA can be approved. CR letters will reflect a complete review and will 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 *Id.* at 10-11.

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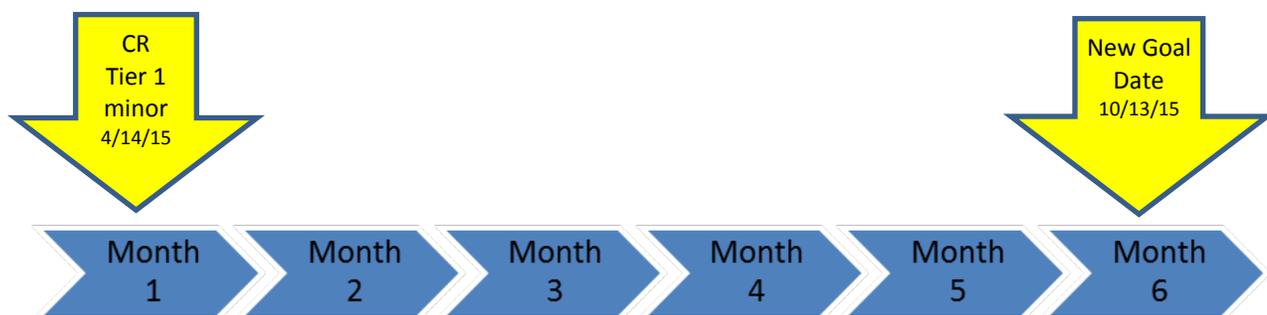
296 As explained in the Commitment Letter, all amendment metric goals are incremental, and the
297 time periods specified are calculated from the date of submission. Thus, the performance metric
298 goal for an amendment to a PAS will be added to the original goal date for that PAS.
299

300 The Commitment Letter explains in more detail the performance metric goals for each
301 amendment tier, which are not repeated here. However, following are some examples of how an
302 amendment to a PAS can have an impact on the GDUFA goal date for that PAS. If an
303 amendment to a PAS is submitted after the issuance of a CR letter, this sets a new goal date for
304 the PAS. For example:
305

- 306 • If a Tier 1 major amendment with a 10-month metric is submitted on February 1, 2016, in
307 response to a CR letter for a PAS, this establishes a new GDUFA goal date of 10 months
308 from the date of submission of the major amendment for that PAS. The new goal date is
309 November 30, 2016.
310



- 319 • If a Tier 1 minor amendment with a 6-month metric is submitted on April 14, 2015, in
320 response to a CR letter for a PAS, this establishes a new GDUFA goal date of 6 months
321 from the date of submission of the minor amendment for that PAS. The new goal date is
322 October 13, 2015.
323



334 Any subsequent amendments submitted to a PAS after the issuance of a CR letter can also adjust
335 the goal date for the PAS and can add time to the review clock.
336

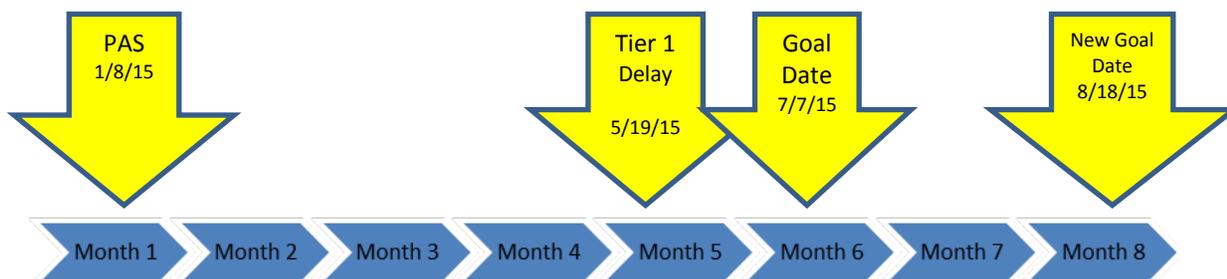
337 If an amendment to a PAS is submitted before the issuance of a CR letter, this can adjust the goal
338 date for the original PAS. For example:
339

- 340 • A PAS with a 6-month metric is submitted on January 8, 2015, and given a goal date of
341 July 7, 2015. A Tier 1 delaying amendment with a 3-month metric is submitted in month

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5 of the original review cycle on May 19, 2015. Submission of the amendment adjusts the GDUFA review clock and extends the goal date 3 months from May 19, 2015, the date of submission of the amendment for that PAS. The new goal date is August 18, 2015.



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.³⁸

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. Other Matters

1. Grouped Supplements

Grouped supplements are multiple supplements (typically five or more) submitted to ANDAs by a single applicant for the same chemistry, manufacturing, and controls (CMC) change to each application. Multiple PAS submissions are categorized as a *grouped supplement* if they (1) cover an identical CMC change to each ANDA; (2) are submitted by the same ANDA applicant; (3) have the same date of submission; and (4) do not include unique data for each supplement.

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.³⁹ 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 a group PAS identifies a lead supplement 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

³⁸ For more detail on administrative amendments, see the draft guidance for industry *ANDA Submissions — Amendments and Easily Correctable Deficiencies Under GDUFA*.

³⁹ 21 USC 379j-42(a)(3) (a PAS is subject to a fee “for each such submission”).

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383 be received, but the other supplements without the requisite paid fee cannot be received. If the
384 other fee-deficient supplements are then submitted at a later date, this can result in different
385 GDUFA goal dates for the supplements initially received and the subsequently filed
386 supplements.

387
388 In lieu of submitting multiple PASs for the same change, in some cases, the ANDA applicant
389 might have the option to submit a PAS with a comparability protocol that outlines the rationale
390 for the change and what studies, data, and information are available to support the change.⁴⁰ The
391 protocol would include a proposed reporting category for submission of future supplements for
392 the same change to different ANDAs.⁴¹ Once the PAS is approved, the agreed-upon reporting
393 category could be used. Thus, at the time the PAS containing the comparability protocol is
394 approved, FDA can designate, where appropriate, a reduced reporting category for future
395 reporting of changes covered by the approved comparability protocol (e.g., from a PAS to a
396 CBE-30 supplement). The GDUFA performance metric goals and applicable user fees would
397 apply to the initial PAS, but not to the future supplements submitted under the reduced reporting
398 category.

399

400 2. *Incorrect Reporting Category*

401

402 If FDA finds that a supplement submitted as a CBE supplement should have been submitted as a
403 PAS, it will notify the applicant. The applicant is not required to withdraw the CBE supplement
404 because when FDA sends a letter explaining that the applicant's submission is not accepted as a
405 CBE supplement, FDA administratively closes the CBE supplement, and it is considered
406 withdrawn. The applicant may resubmit the supplement as a PAS for FDA approval before
407 distribution of the drug product, along with the required GDUFA user fee.⁴² The GDUFA
408 performance metric goals and applicable user fees will apply to that PAS.⁴³ As explained in
409 section III.B, the GDUFA review clock will start from the date of submission of that PAS. For
410 example:

411

- 412 • An applicant submits a CBE supplement on November 17, 2014. FDA determines that
413 the applicant should have submitted the supplement as a PAS and notifies the applicant
414 that the proposed change was submitted incorrectly as a CBE supplement. Upon issuance
415 of the letter explaining that the applicant's submission is not accepted as a CBE
416 supplement, FDA considers the CBE withdrawn. On December 1, 2014, the applicant
417 resubmits the supplement as a PAS, which meets all the submission requirements,

⁴⁰ A comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific CMC changes in the identity, strength, quality, purity, and potency of a specific drug product as these factors relate to the safety and effectiveness of the product. See the draft guidance for industry *Comparability Protocols — Chemistry, Manufacturing, and Controls Information* at 3 (draft comparability guidance), available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070545.pdf>.

⁴¹ Id. at 12.

⁴² § 314.70(c)(5)(i).

⁴³ Draft GDUFA user fee Q&A guidance at 13, *supra* note 6.

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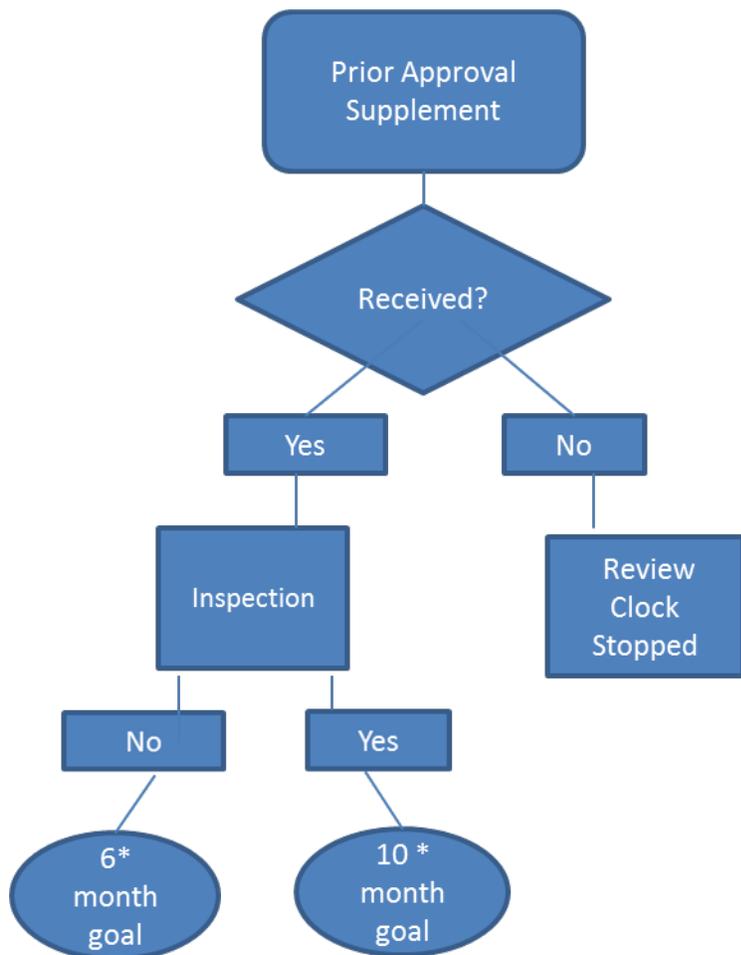
418 including the applicable GDUFA user fee. The GDUFA review clock commences on
419 December 1, 2014.
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APPENDIX A – GDUFA SUPPLEMENTS FLOW CHART



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* If an amendment is filed to the supplement, it may change the goal date. See guidance for industry, *ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA*, Flow Chart at Appendix D. 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 be changed to a 10-month goal date if, during the review, an inspection is deemed necessary.