Guidance for Industry

ANDA Submissions — Amendments and Easily Correctable Deficiencies 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DRAFT GUIDANCE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
Generic Drugs

Guidance for Industry

ANDA Submissions — Amendments and Easily Correctable Deficiencies Under GDUFA

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U.S. Department of Health and Human Services
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Guidance for Industry[1]
ANDA Submissions — Amendments and Easily Correctable Deficiencies Under GDUFA

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist applicants preparing to submit to the Food and Drug Administration (FDA) amendments to abbreviated new drug applications (ANDAs) or prior approval supplements (PASs) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act),[2] by explaining how the performance metric goals established as part of the Generic Drug User Fee Amendments of 2012 (GDUFA)[3] apply to these submissions. Specifically, this guidance does the following:

- Describes the Tier system for the different types of amendments
- Explains how different types of amendments may affect the application's original review dates
- Explains FDA's performance metric goals based on the different amendment Tiers
- Explains the process for submitting amendments
- Describes the request for reconsideration process for FDA classification decisions

When finalized, this guidance will replace the December 2001 guidance for industry *Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications*[4] in consideration of the new amendment review Tier system and performance goals under GDUFA.

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

[2] See 21 U.S.C. 355(j).

[3] See also the draft guidance for industry *ANDA Submissions — Prior Approval Supplements Under GDUFA*. When finalized, the guidance will represent the FDA's current thinking on this topic. Examples of amendments submitted to ANDAs in this guidance also apply to amendments to PASs.

[4] The guidances referenced in this document are available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update

FDA's guidance documents, including this guidance, 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, GDUFA was signed into law by the President.[5] GDUFA is designed to speed the delivery of safe and effective generic drugs to the public and reduce costs to industry. GDUFA is based on an agreement negotiated by FDA and representatives of the generic drug industry 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 enhancements to the performance of FDA's generic drugs program and to bring greater predictability and timeliness to the review of generic drug applications.

In accordance with a Commitment Letter[6] that accompanied the legislation, FDA agreed to certain performance goals and procedures for the review of amendments submitted electronically to original ANDAs and PASs filed on or after October 1, 2014. The performance goals do ***not*** apply to amendments submitted on or after October 1, 2014, if they amend original ANDAs or PASs submitted before October 1, 2014.

For purposes of FDA's performance goals, the Commitment Letter classified amendment types into Tiers, which have associated performance metric goals, some of which will extend the applications original review date. Each Tier has corresponding performance metric goals, ranging from a 3-month review clock to no goal date, depending on the amendment's classification. The Tier system takes the following factors into consideration:

- Whether an amendment is solicited or unsolicited
- Whether it is major or minor
- The number of amendments submitted to the ANDA or PAS
- Whether an inspection is necessary to support the information contained in the amendment

guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page.

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

[6] GDUFA: Human Generic Drug Performance Goals and Procedures Fiscal Years 2013 through 2017 (Commitment Letter), available at http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf.

Performance metric goals establish predictability in FDA's review process. The Tier system creates strong incentives for applicants to submit high-quality original submissions. Incomplete or poor-quality applications often result in multiple review cycles that extend or eliminate the review clock altogether. For example, if an applicant must submit a second major amendment to an application, that application loses its review goal date. Applicants are strongly encouraged to submit complete, high-quality original applications, making later amendments unnecessary.

III. CATEGORIES OF GDUFA AMENDMENTS

FDA's performance goal obligations under GDUFA start when an amendment is submitted to FDA. This is the date the amendment arrives in the appropriate FDA electronic portal.[7] As described in the Commitment Letter, the performance goals identified in this guidance apply only to those amendments submitted to ANDAs that have been submitted in or after fiscal year (FY) 2015 (on or after October 1, 2014).

Descriptions of *major* and *minor* in this guidance apply only to the classification of major and minor amendments and are distinguishable from other major or minor issues that may be identified by FDA staff (e.g., a filing deficiency that is identified after an ANDA is submitted by the applicant, but before it is received by FDA and assigned for review). The following table highlights the three Tiers of solicited and unsolicited amendments with their respective performance review goals. As indicated, amendments may add review time to the original ANDA review goal date, but in no case do amendments shorten the original goal dates.[8] More specific definitions are provided in the sections following the table.

	Solicited Amendment Goals	**Unsolicited Amendment Goals**
TIER 1	1st Major: 10 months 1st – 3rd Minor: 3 months* 4th – 5th Minor: 6 months*	*Delaying action* or otherwise would eventually be solicited: 3 months*
TIER 2	N/A	Amendment not arising from "delaying action": 12 months
TIER 3	≥ 2nd Major: No goal ≥ 6th Minor: No goal	N/A

*10 months if inspection required

[7] Commitment Letter at 16; see also the draft guidance for industry *Providing Regulatory Submissions in Electronic Format — Receipt Dates* (Feb. 2014). These submissions are deemed to be submitted to FDA on the day when 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 that case, the submission is deemed to be submitted on the next day when that office is open for business.

[8] Commitment Letter at 10.

A. What Is a Solicited Amendment?

A solicited amendment is a submission made by an applicant in response to a complete response letter (CR) issued by FDA. After completing a technical review of an ANDA, FDA may issue a complete response (CR) letter identifying deficiencies from review disciplines and requesting certain information from the applicant to correct those deficiencies. The applicant's response to FDA's CR letter is a solicited (nongratuitous) amendment. Solicited amendments are classified as either Tier 1 or Tier 3. (See section IV of this guidance for the performance goals associated with the Tiers.) Solicited amendments are classified as either a major amendment, a minor amendment, or an easily correctable deficiency (ECD).

1. What is a major amendment?

Major amendments contain a substantial amount of new data or new information not previously submitted to or reviewed by FDA, requiring, in FDA's judgment, a substantial expenditure of FDA resources. In general, the type, quantity, or complexity of data contained in a major amendment requires a lengthy review by FDA, and consults from other divisions or offices may be required to complete the review. For example, a major amendment could contain a new analysis or a major reanalysis of studies previously submitted. Examples of major amendments are those that contain a new batch, a new analytical method, a new bioequivalence study, or a new validation method to support approval of the pending application.

The first solicited major amendment is classified as Tier 1; any solicited major amendment subsequent to the first is classified as Tier 3. Appendix A of this guidance contains a nonexhaustive list of deficiencies, categorized by discipline, that are generally classified as major amendments.

2. What is a minor amendment?

FDA review of a minor amendment requires, in FDA's judgment, fewer FDA resources than are necessary to review a major amendment, but more than are necessary to review the information submitted in response to an ECD. An example of a minor amendment is a submission to address missing information that would not require new studies. The first through fifth solicited minor amendment is classified as Tier 1; any solicited minor amendment subsequent to the fifth minor amendment is classified as Tier 3. Appendix B of this guidance contains a nonexhaustive list of deficiencies, categorized by discipline, that are generally classified as minor amendments.

3. What is an easily correctable deficiency (ECD)?

FDA review of information submitted in response to an ECD requires, in FDA's judgment, a modest expenditure of FDA resources. An applicant should be able to respond to an ECD quickly as the applicant should already possess or be able to quickly retrieve the information needed for an adequate response to an ECD. ECDs routinely include requests for clarification of data already submitted, requests for postapproval commitments, or final resolution of technical

issues. ECDs do not extend the current goal date. Appendix C of this guidance contains a nonexhaustive list of deficiencies, categorized by discipline, that are generally classified as ECDs.

B. What Is an Unsolicited Amendment?

An unsolicited (gratuitous) amendment is submitted on the applicant's own initiative and not in response to FDA's CR letter. Unsolicited amendments are categorized as either delaying or nondelaying. All delaying unsolicited amendments are classified as Tier 1 amendments.[9] All non-delaying unsolicited amendments are classified as Tier 2 amendments.

1. What is a delaying amendment?

Delaying amendments[10] address actions by a third party that would cause delay or impede application review or approval timing and that were not a factor at the time of submission.[11] These kinds of amendments might contain information that FDA would otherwise ask for as a result of post ANDA submission reference listed drug (RLD) changes or changes to the drug master file (DMF). For example, delaying amendments include applicant submissions to address:

- Changes to the RLD's labeling or updates to the United States Pharmacopeia (USP) monograph
- Risk Evaluation and Mitigation Strategies (REMS) and REMS modifications
- Generic approval requirements reflected in citizen petition responses issued by FDA[12]

As stated in the Commitment Letter, FDA has broad discretion to determine what constitutes a delaying event caused by actions generally outside of the applicant's control, taking into account facts and information supplied by the ANDA applicant.[13] Unsolicited amendments that are in response to a delaying action or that FDA would eventually solicit are classified as Tier 1 delaying amendments.[14] Delaying amendments do not add to the count of major or minor amendments for the purpose of classification.

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[9] Commitment Letter at 10.

[10] The phrase *delaying amendment* refers to an amendment that is the result of a delaying action. As explained in this guidance, the performance metric for a delaying amendment (3 months) is actually shorter than the metric for a nondelaying amendment (12 months). These terms are used to reflect their use in the Commitment Letter.

[11] Commitment Letter at 10 and 14.

[12] For example, if a CP requests certain BE data be submitted to support an ANDA for a particular drug product and FDA grants that petition, an ANDA applicant may submit the BE data reflected in the CP response prior to FDA's request of the data from the ANDA applicant. Such amendment would be considered a Tier 1 delaying amendment.

[13] Commitment Letter at 10.

[14] Id. at 10.

2. What is a nondelaying amendment?

Nondelaying amendments are unsolicited amendments that contain information that is not requested by FDA and is not the result of changes to the RLD or USP monograph, changes to the RLD labeling, a REMS and REMS modification, or generic approval requirements reflected in citizen petition responses issued by FDA. Examples of nondelaying amendments include submission of new data to address an original incomplete data submission or new information such as the addition of a new strength of the product or a new manufacturing facility. Nondelaying amendments are classified as Tier 2 amendments.

C. What Is an Administrative Amendment?

Administrative amendments are routine in nature and do not require scientific review. Requests for final approval with no scientific changes to the ANDA, patent amendments,[15] and general correspondence submitted by applicants are generally considered administrative amendments. 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.

IV. GDUFA PERFORMANCE METRIC GOALS FOR AMENDMENT TIERS

A. What Are Amendment Tiers?

The Commitment Letter outlines the performance metrics for amendments. As explained in the Commitment Letter, all amendment goal dates are incremental,[16] and the time periods specified are calculated from the date of submission of the amendment. Review time is added to the original ANDA review goal date, but in no case do amendments shorten the original goal dates.[17] Amendments are grouped as Tier 1, Tier 2, or Tier 3. The Tier type determines how review goals apply to the amendments.[18]

1. What is a Tier 1 amendment?

[15] We note that certain information that may be submitted in a patent amendment may require further and more detailed review. For example, additional review may be required if an ANDA applicant submits a patent amendment notifying FDA that it is not seeking approval for a method of use protected by patent or exclusivity by the RLD under section 505(j)(2)(A)(viii) of the FD&C Act. When submitting a patent amendment, applicants should consider whether the submission contains any additional information that would be classified as a nondelaying Tier 2 amendment.

[16] The Commitment Letter uses the terms *incremental* and *additive*. FDA interprets both terms as having the same meaning for purposes of determining goal dates.

[17] Commitment Letter at 10.

[18] Id. at 10-12.

Tier 1 amendments include the first solicited major amendment, the first five solicited minor amendments, and all delaying amendments.[19]

2. What are the performance metric goals associated with Tier 1 amendments?

FDA commits to reviewing and acting[20] on a certain percentage of first major amendment submissions within a certain time period from the date of submission.[21] The percentages and time periods vary by FY cohort depending on the fiscal year in which the original ANDA or PAS was submitted. The GDUFA program is structured based on cohorts of submission dates corresponding to the 5 fiscal years to be covered in the program. The year-3 cohort refers to the dates of submissions made electronically in FY 2015; the year-4 cohort refers to submissions made electronically in FY 2016; the year-5 cohort refers to submissions made electronically in FY 2017.[22]

- FDA will review and act on 60% of first major amendment submissions within 10 months from the date of submission for the year-3 cohort.
- FDA will review and act on 75% of first major amendment submissions within 10 months from the date of submission for the year-4 cohort.
- FDA will review and act on 90% of first major amendment submissions within 10 months from the date of submission for the year-5 cohort.

Similarly, FDA commits to reviewing and acting on a certain percentage of minor amendment submissions within a certain time period from the date of submission. The percentages and time periods vary by fiscal year and depend on the total count of amendments submitted to an application.

First Through Third Minor Amendment Submissions:

- FDA will review and act on 60% of first through third minor amendment submissions within 3 months from the date of submission for the year-3 cohort.
- FDA will review and act on 75% of first through third minor amendment submissions within 3 months from the date of submission for year-4 cohort.

[19] As stated elsewhere in this document, delaying amendments are all unsolicited amendments indicated by applicant and agreed by FDA to be a result of either delaying actions or that would eventually be solicited.

[20] An *action* on a submission can be FDA issuing a CR letter, an approval letter, a tentative approval letter, or a refuse-to-receive action. Commitment Letter at 14.

[21] Consistent with our interpretation of "from the date of" submission under the FD&C Act and our regulations, we interpret this language in the Commitment Letter to mean that calculation of the goal date starts on the receipt date of the submission (see footnote 9). Also, according to the language in the Commitment Letter, we will calculate the goal date in months. We note that this calculation differs from the calculation of goal dates agreed to under the Prescription Drug User Fee Act ("PDUFA") as set forth in the PDUFA Commitment Letter, which contains different language from the language in the GDUFA Commitment Letter. See PDUFA Commitment Letter, available at http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf.

[22] Commitment Letter at 14.

- FDA will review and act on 90% of first through third minor amendment submissions within 3 months from the date of submission for the year-5 cohort.

Fourth and Fifth Minor Amendment Submissions:

- FDA will review and act on 60% of fourth through fifth minor amendment submissions within 6 months from the date of submission for the year-3 cohort.
- FDA will review and act on 75% of fourth through fifth minor amendment submissions within 6 months from the date of submission for year-4 cohort.
- FDA will review and act on 90% of fourth through fifth minor amendment submissions within 6 months from the date of submission for the year-5 cohort.

Exception:

- Any Tier 1 amendment requiring an inspection has a 10-month metric.

FDA's goal for review of a delaying amendment is 3 months, unless the amendment raises issues for which an inspection may be required, in which case the goal is 10 months.

3. What is a Tier 2 amendment?

Tier 2 amendments include all unsolicited amendments that are not classified as Tier 1 delaying amendments.[23]

4. What are the performance metric goals associated with Tier 2 amendments?

FDA commits to reviewing and acting on a certain percentage of Tier 2 amendment submissions within a certain time period from the date of submission. The percentages and time periods vary by FY cohort.

- FDA will review and act on 60% of Tier 2 amendment submissions within 12 months from the date of submission for the year-3 cohort.
- FDA will review and act on 75% of Tier 2 amendment submissions within 12 months from the date of submission for year-4 cohort.
- FDA will review and act on 90% of Tier 2 amendment submissions within 12 months from the date of submission for the year-5 cohort.

5. What is a Tier 3 amendment?

Tier 3 amendments include all solicited major amendments subsequent to the first major amendment and all solicited minor amendments subsequent to the fifth minor amendment.

6. What are the performance metric goals associated with Tier 3 amendments?

[23] Id. at 10 and 14.

There are no GDUFA performance goals for Tier 3 amendments.

B. How Are the Amendment Goals Applied?

Performance metric goals are applied to the date of submission of the amendment; amendment goals may or may not change the original ANDA's review goal date.[24] Amendments submitted during the application review either extend or do not change the ANDA goal date.

1. Which amendments are subject to the performance metric goals described in this guidance?

The cohort year of the original ANDA or PAS determines the subsequent amendment's performance metric goals. Only ANDAs and PASs filed in cohort years 3 through 5 (FYs 2015, 2016, and 2017) are assigned goal dates. Accordingly, the amendment goal dates apply to only those applications filed in cohort years 3 through 5. In other words, the amendment performance metric goals described in this guidance do not apply to an amendment submitted in FY 2015, 2016, or 2017 if the original ANDA or PAS was submitted before FY 2015.

> *Example:* An original application is filed on September 1, 2014. On September 1, 2015, the applicant submits an unsolicited amendment to its pending application. Neither the application nor the amendment has goal dates.

> *Example:* An original application is filed on September 1, 2014. On September 1, 2015, FDA issues a CR letter. On March 1, 2016, the applicant submits a CR amendment to the application. No goal date is assigned to this amendment.

Performance metric goals apply only to amendments submitted electronically.[25]

2. For purposes of applying the GDUFA performance metric goals, are cohort years assigned by date of submission of the ANDA or the most recent amendment to the ANDA?

Cohort years are assigned by date of submission of the original ANDA. Once an ANDA is submitted and designated a particular cohort year, the submission of a subsequent amendment does not change the cohort year.[26] Any additional review times resulting from the submission of amendments may be added to the original goal date. In no case, does the submission of an amendment shorten the goal date for that ANDA.

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[24] Id. at 10.

[25] Commitment Letter at 7.

[26] Id. at 10.

Because amendment performance goals are incremental and may extend the original goal date, and because submission of multiple amendments may result in a Tier 3 classification with no GDUFA metric goals, FDA strongly encourages applicants to submit complete applications, making later amendments unnecessary.

3. When will an application lose its goal date?

If an applicant submits an amendment and that amendment is classified as a Tier 3 amendment (e.g., the 2nd major amendment or 6th minor amendment), the ANDA will lose its goal date.

> *Example:* In response to a CR letter, an applicant submits an amendment (CR amendment) that is classified as a Tier 1 solicited major amendment. FDA reviews the amendment and, in a second CR letter, identifies major deficiencies that must be corrected before approval. When the applicant submits a second major amendment in response to the second CR letter, the application loses its goal date.

> *Example:* In response to a CR letter, an applicant submits an amendment that is classified as a Tier 1 solicited minor amendment. FDA reviews the amendment and, in a second CR letter, identifies major deficiencies that must be corrected before the application may be approved. The applicant submits a second CR amendment that is classified as a Tier 1 solicited major amendment. FDA reviews the amendment and, in a third CR letter, identifies major deficiencies that remain uncorrected. When the applicant submits the second major amendment in response to the third CR letter, the application loses its goal date.

4. How are goal dates calculated when an amendment is submitted before a CR letter is issued?

An amendment submitted before a CR letter is issued adjusts the goal date for the original application and is additive. Subsequent amendments submitted before a CR letter is issued also adjust the goal date for the application and are additive.[27] FDA has discretion to accept an unsolicited amendment submitted during the review cycle and adjust the goal date for the application. In the alternative, FDA may defer review of the unsolicited amendment, issue the CR letter, and review the unsolicited amendment when the applicant submits the CR amendment. If review of a Tier 2 unsolicited amendment is deferred, the goal date is adjusted to 12 months from the date of submission of the CR amendment.

> *Example:* An unsolicited amendment with a 12-month review metric submitted 4 months prior to the original goal date adds 8 months to the review clock.

[27] Id. at 10.

Example: A delaying amendment with a 3-month review metric submitted 4 months prior to the original goal date does not alter the review clock.

Example: An unsolicited amendment with a 12-month review metric submitted 1 month prior to the original goal date is deferred until after FDA issues the CR letter and the applicant submits the corresponding CR amendment. The new goal date for the CR amendment and the unsolicited amendment is 12 months from the date of the CR amendment.

Example: A delaying amendment with a 3-month review metric is submitted 1 month prior to the original goal date. FDA adds 2 months to the review clock and reviews the delaying amendment before taking action on the application.

5. How are goal dates calculated when an amendment is submitted in response to a CR letter?

Generally, an amendment submitted after a CR letter is issued sets a new goal date for the application and subsequent amendments submitted after the CR letter is issued also adjust the goal date for the application and are additive.[28]

Example: A CR amendment is submitted in response to minor deficiencies identified in a CR letter. It is the application's second solicited minor amendment. That amendment has a 3-month metric from the date of submission.

Example: An applicant submits a CR major amendment, which has a 10-month review metric. In month 4 of FDA's review of the major CR amendment, the applicant submits an unsolicited amendment; that amendment has a 12-month metric that is added to the date of submission, adding 6 months to the original goal date.

6. What happens when there are multiple factors affecting the goal date calculation?

If an amendment contains multiple elements, the longest goal date applies to the review goal.[29]

7. How are goal dates calculated when an applicant submits an amendment to an original ANDA before the ANDA has been received?

Amendments submitted during filing review of the ANDA are classified as Tier 2 unsolicited amendments. If the ANDA is submitted in the year-3 or year-4 cohort[30] and is received, review

[28] Id. at 10.

[29] Commitment Letter at 10.

of the ANDA and the unsolicited amendment will have a 15-month goal date because the longest goal date applies (in this case, the goal date for the ANDA). If the ANDA is submitted in the year-5 cohort and is received, review of the ANDA and the unsolicited amendment will have a 12-month goal date from the date of submission of the unsolicited amendment.

> *Example:* An applicant submits an original ANDA on October 1, 2016 (year-5 cohort). On November 1, 2016, during filing review of the ANDA, the applicant submits an unsolicited amendment to the ANDA. The goal date for that ANDA is adjusted from July 31, 2017 (10-month review metric for year-5 cohort ANDAs), to October 31, 2017, which is 12 months from the date of submission of the unsolicited amendment.

8. How are goal dates calculated when an applicant submits an unsolicited amendment after a CR letter is issued but before the applicant responds to the CR letter?

Review of any Tier 2 unsolicited amendments received in the period between FDA's issuance of a CR letter and the applicant's submission of its CR amendment is deferred until the CR amendment is received. The application will be assigned a 12-month metric calculated from the date of submission of the CR amendment.

> *Example:* An applicant receives a CR letter identifying several minor deficiencies. Before submitting the CR amendment, the applicant submits an unsolicited non-delaying amendment. FDA will defer review of the unsolicited non-delaying amendment until the applicant submits a CR amendment that responds to the deficiencies identified in the CR letter. The CR amendment is considered the applicant's second minor amendment and is subject to a 3-month review metric. However, based on the unsolicited non-delaying amendment, the goal date is adjusted to 12 months calculated from the date of submission of the CR amendment, because the longest applicable goal date applies.

9. How are goal dates calculated for amendments to tentatively approved applications?

According to the Commitment Letter, a request for final approval is an example of an administrative amendment.[31] If an applicant has made no changes to product or process since the tentative approval was granted, FDA would not need to dedicate a significant amount of resources to ensure the product is eligible for final approval and would not set a new goal date

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[30] As stated in the Commitment Letter at page 9: FDA will review and act on 60%t of original ANDA submissions within 15 months from the date of submission for the year-3 cohort. FDA will review and act on 75% of original ANDA submissions within 15 months from the date of submission of the year-4 cohort. FDA will review and act on 90% of original ANDA submissions within 10 months from the date of submission for the year-5 cohort.

[31] Commitment Letter at 10.

for review. Most standard requests for final approval, in which few or no changes have been made to the application since the tentative approval, including acceptable compliance (good manufacturing practices (GMP)) status of applicable facilities, will be reviewed in approximately 3 months. However, if, in the time between tentative approval and the request for final approval, the applicant has made changes to product or process (i.e., change in validation procedures, change in manufacturing facilities), this information may warrant a more thorough review. Thus, if an applicant with a tentatively approved application requests final approval, but includes information in the amendment that would cause the amendment to meet the definition of an unsolicited non-delaying amendment, FDA will consider the amendment to be both a request for final approval and an unsolicited non-delaying amendment, which would set a goal of 12 months. As explained in the Commitment Letter[32] and question 6 of this section, the longest applicable review date will apply to amendments with multiple elements.

OGD staff will review the content of the request for final approval to determine whether the submission is classified as an administrative amendment or as a Tier 2 unsolicited non-delaying amendment. If the amendment is classified as a Tier 2 unsolicited non-delaying amendment, OGD will act upon the amendment within 12 months from receipt.

> *Example:* An applicant was granted tentative approval to an original application submitted after October 1, 2014, and submits on August 1, 2017, a request for final approval that identifies a change in the manufacturing facility. FDA will have until July 31, 2018, to review the request for final approval.
>
> *Example:* An applicant was granted tentative approval to an original application submitted after October 1, 2014, and submits on August 1, 2017, a request for final approval that includes a Tier 1 delaying amendment (e.g., RLD labeling update). FDA will have until October 31, 2017, to review the delaying amendment and the request for final approval.

10. If my application qualifies for expedited review, what is the impact of that expedited status on the GDUFA metric goals for any subsequent amendments?

As stated in the Commitment Letter, certain submissions may be granted expedited review. Amendments to expedited applications are subject to GDUFA performance metric goals in the same way as amendments to nonexpedited applications. If a submission has been granted expedited status, review may be completed before the applicable GDUFA goal date.

11. Under what circumstances can FDA change the classification of an applicant's CR amendment?

The type, quantity, or complexity of data submitted in an amendment may prompt a change in classification of the amendment to ensure appropriate allocation of FDA resources for review.

[32] Commitment Letter at 10.

All initial classifications and changes to classifications will be made at FDA's discretion. A CR letter will advise the applicant whether the CR amendment will be classified as a major or minor amendment. However, if the applicant submits a CR amendment that contains additional information or data beyond what was identified in the CR letter as necessary to correct the deficiency or deficiencies identified in the CR letter, FDA will change the classification of the amendment from a Tier 1 solicited major or minor amendment to a Tier 2 unsolicited amendment.

> *Example:* An applicant receives a CR letter identifying certain deficiencies in an application. The CR letter states that the CR amendment will be considered a minor amendment with a 3-month review metric (Tier 1). The applicant submits an amendment and identifies it as a minor CR amendment. However, in lieu of correcting a deficiency using the strength of the drug product that is the subject of the application, the applicant elects to use a new strength. Data supporting the new strength are included in the CR amendment. FDA changes the classification of this amendment from Tier 1 minor amendment to a Tier 2 unsolicited amendment with a 12-month review metric.

FDA's reclassification of a minor or major CR amendment to an unsolicited amendment will not affect the amendment count that would have applied to the amendment if the sponsor had not submitted additional information. For example, if the CR letter advises a sponsor that the responsive amendment will be classified as a minor amendment, and the sponsor submits an amendment with additional elements that FDA reclassifies as a Tier 2 unsolicited amendment, the amendment will still count toward the sponsor's total minor amendment count.

12. Under what circumstances can FDA change the classification of an applicant's ECD response?

If a response to an ECD is not provided within 10 business days from the request, FDA may reissue the ECD as a minor deficiency in the CR letter upon completion of the current review cycle. Furthermore, if the response to an ECD was filed within 10 business days but contains information requiring more extensive review than is typically required of ECDs, the amendment will be classified as a minor amendment and the goal date adjusted accordingly.

> *Example:* An applicant fails to submit their ECD response within 10 business days from the request. In its discretion, FDA may defer review of the submission and add the request as a minor amendment to the next CR letter.

> *Example:* An applicant submits a response to the ECD and that submission contains unsolicited information. FDA will change the classification of the ECD response to a Tier 2 unsolicited non-delaying amendment subject to a 12-month metric, calculated from the date of the newly classified submission.

> *Example:* An applicant submits a response to an ECD within 10 business days from the request. The submission directly responds to the ECD request but does

so with information requiring a more extensive review than is typically required of ECDs. FDA may change the classification of the submission to a minor amendment and set the appropriate goal date based on the amendment count.

13. If an applicant provides a minor CR amendment in response to a CR letter within 10 business days, can FDA classify the submission as an ECD?

As stated earlier, whether a submission is classified as a minor amendment or an ECD depends on the extensiveness of FDA resources required to review the submission. Appendix B provides examples of deficiencies listed by discipline that would generally result in a minor amendment. The information or data necessary to correct these deficiencies require more FDA resources to review than an ECD, so the classification as a minor amendment will not change. We also note that a solicited amendment in response to a CR letter sets a new goal date for that application. Submission of an ECD would not set or adjust the goal date for an application, and in no case can the submission of an amendment shorten the goal date.

Example: An applicant receives a CR letter noting minor deficiencies that must be addressed. Within 10 business days of receipt of the CR letter, the applicant submits a CR amendment and requests that the submission be classified as an ECD. Because the CR amendment was classified as a minor amendment in consideration of the FDA resources required to review the submission, FDA will not change the classification of the minor CR amendment.[33]

14. What process will FDA use when changing the classification of amendments?

The decision to change the classification of an amendment will be made by the regulatory project manager (RPM) and the ANDA review team in consultation with the appropriate division director. Notification of a change in classification will be provided in writing as soon as is practicable after FDA determines that the change is appropriate. Reconsideration of a decision to change the classification of an amendment may be requested using the process described in section VI of this guidance.

15. How will FDA handle amendments to applications that are of overall poor quality and amendments of overall poor quality?

As stated earlier, an amendment responding to multiple deficiencies that, in the aggregate, requires a substantial expenditure of FDA resources to review will be classified as a solicited major amendment. Such classification will occur if an application is of such overall poor quality that a substantive review cannot be performed with the information or data provided — and the

[33] In this guidance, FDA describes the process for requesting reconsideration of amendment classification. Applicants can only request reconsideration of a major amendment. It is not possible to change the classification of a minor amendment to an ECD because an ECD is not part of the amendment Tier structure under GDUFA and, furthermore, because the review cycle has been closed by FDA by taking the action of issuing the complete response letter.

type, quantity, or complexity of the information or data required to correct the identified deficiencies will require extensive review by FDA. Similarly, if an applicant's amendment responding to minor deficiencies is so poorly crafted that substantive review will require, in FDA's judgment, a greater expenditure of resources than is traditionally required for review of a minor amendment, FDA will change the classification of the amendment from minor to major.

FDA may, in its discretion, decide not to change the classification of a minor amendment of overall poor quality if the minor amendment causes the application to lose its goal date.

> *Example:* An applicant receives a CR letter from FDA identifying multiple deficiencies in the application. Although each deficiency, by itself, may not require a substantial expenditure of FDA resources to review, the application is of such overall poor quality that FDA determines that review of the CR amendment will require extensive FDA resources. Assuming this will be the applicant's first major amendment, FDA classifies this CR amendment as a Tier 1 solicited major amendment with a 10-month review metric.
>
> *Example:* An applicant receives a CR letter from FDA indicating that the amendment should be classified as a minor amendment. Upon review of the CR amendment, FDA finds that the submission is poorly organized, difficult to navigate, and with data not clearly presented. FDA determines that review of this submission will require a significant expenditure of FDA resources. FDA will change the classification of the CR amendment from minor to major and notify the applicant of the change in classification and goal date.
>
> *Example*: An applicant submits the 6th minor amendment to its original ANDA. Upon review, FDA determines that the amendment is such overall poor quality, that FDA would normally change the classification to a major amendment. FDA will not change the classification to a major amendment because the application has already lost its goal date.

16. Which submission types are excepted from the amendment/Tier classification system?

Because positron emission tomography (PET) applications are not subject to the fee collecting provisions of GDUFA,[34] the Tier review classifications and performance metric goals do not apply to amendments submitted to PET applications. Similarly, the performance metric goals do not apply to changes being effected (CBE) supplements, which do not require the payment of a fee under GDUFA.

17. How will FDA determine if an inspection is necessary?

[34] FD&C Act at section 744B(l) (21 U.S.C. 379j–42(l)).

If an applicant submits a Tier 1 amendment that includes information on a new facility or a facility that is being used for a new purpose, the amendment will be assigned a 10-month metric to allow time for an inspection. If an applicant submits a Tier 2 amendment that includes information on a new facility or a facility that is being used for a new purpose, the amendment will be assigned a 12-month metric, as the longest goal date applies.

> *Example:* An applicant submits its first minor (Tier 1) amendment in response to a CR letter (3-month goal) but the manufacturing site requires an inspection (10-month goal). The amendment will have a 10-month review metric.
>
> *Example:* An applicant submits a Tier 1 solicited minor amendment. However, in response to the CR letter, the CR amendment contains information on a facility that is being used for a new packaging line. If the facility requires an inspection, a 10-month review metric will be assigned.
>
> *Example:* An applicant submits a Tier 2 nondelaying amendment that contains information on a new manufacturing site. The amendment will have a 12-month review metric.

V. SUBMISSION OF AMENDMENTS

Any amendment to an original ANDA should identify on the first page of the submission that it is an amendment. 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 amendment is solicited or unsolicited
2. The amendment classification as identified in the CR letter or as proposed by the applicant based on the criteria provided in this guidance (major amendment, minor amendment, administrative amendment, delaying, or nondelaying)
3. The Tier classification (Tier 1, Tier 2, or Tier 3)
4. A statement indicating whether the amendment contains any manufacturing or facilities changes
5. A list of the specific review disciplines to review the amendment (Chemistry, Labeling, DMF, Bioequivalence, Microbiology, or Clinical) and the corresponding amendment Tier (Tier 1 solicited amendment or Tier 2 unsolicited amendment) for each component
6. If expedited review is requested, the statement, *Expedited Review Request* should be placed prominently at the top of the submission. The submission should include a basis for the expedited review request.

VI. RECONSIDERATION OF AMENDMENT CLASSIFICATION

An applicant may request reconsideration of FDA's amendment classification. If an applicant is requesting ***reconsideration of a CR amendment***, the applicant will submit a written request for a post-CR-letter meeting[35] within 10 business days from issuance of the CR letter. The request should be sent to the application with a copy to the RPM. The applicant should clearly state in the meeting request that it is seeking a reconsideration. Before the meeting, the applicant will be asked to submit meeting materials. The materials should contain information adequate to explain the nature of the request, including the following:

1. A comprehensive statement of why FDA should reconsider the classification
2. A statement identifying the division or office that issued the original decision
3. A list of documents previously submitted to FDA that are deemed necessary for resolution
4. The name, title, and contact information (i.e., mailing address, email address, telephone number, and fax number) for the applicant contact for the request

The division will issue a decision about the request for reconsideration and notify the applicant of the decision within 10 business days from the date of the meeting. If the division grants the request for reconsideration after the amendment has been submitted and a review is pending, the change in classification will not alter the goal dates assigned to the amended application. However, the application's amendment count will be adjusted. If the amendment has not yet been submitted, the amendment will be assigned the revised classification and corresponding goal date. The applicant's CR amendment should clearly identify the new classification and state that the amendment classification was changed by the division.

If an applicant wishes to request ***reconsideration of a change in classification that occurred after submission of the applicant's CR amendment***, the applicant should submit a request for reconsideration within 10 business days from issuance of the goal letter. The applicant should submit a written request for reconsideration to the application and a copy to the RPM. The request should contain information adequate to explain the nature of the dispute, as described above. The division will review the information submitted by the applicant and determine whether the request for reconsideration will be granted or denied. The division will notify the applicant of the decision within 10 business days from the date the request for reconsideration was received. If rendered, a change in classification will not alter the goal dates assigned to the amended application. However, the application's amendment count will be adjusted.

All reconsideration decisions will be made by the discipline's division director. If an applicant disagrees with the outcome of the reconsideration, the applicant may initiate a formal appeal.[36] Any applicant seeking an appeal *above* the division level should first seek reconsideration *at* the division level (21 CFR 314.103).

[35] The post-CR letter meeting and any meeting held to discuss a request for reconsideration will generally be a teleconference.

[36] 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, this guidance will represent FDA's perspective on the issue.

APPENDIX A — EXAMPLES OF MAJOR AMENDMENTS

1. *Type II Drug Master File (DMF)*

- Identity of the active pharmaceutical ingredient (API) and/or equivalence to the reference listed drug (RLD) are not established
- Starting material is inappropriate
- Unqualified impurity if toxicology studies are required to qualify
- New analytical methods are needed because method is not stability indicating, fails to adequately resolve analytes, or is not sensitive enough for its intended purpose, and significant method changes are necessary
- Sterility assurance or adventitious agent removal studies are not provided when required (see list for *5. Microbiology*)
- Reference is made to a secondary DMF that is not submitted or not in active status

2. *Chemistry*

- Unqualified impurity levels if toxicology studies are required to qualify
- New source of API is needed
- New site of the finished dosage form (FDF) manufacture is needed
- Unacceptable physical properties
- Need for full-term stability to establish expiration dating because of failing accelerated and intermediate data
- New packaging system is needed when system is not properly delivering the proper dose
- New analytical methods are needed because method is not stability indicating or is not sensitive enough, and significant method changes are necessary
- Critical quality attributes are not identified or controlled
- Environmental assessment is not provided for plant-derived products
- Uncorrected DMF deficiencies

3. *Bioequivalence*

- Request for additional validation data (i.e., cross-validation of accuracy and precision in the presence of different anticoagulants)
- Justification for Office of Scientific Investigations (OSI) findings
- Questions concerning exclusion of subjects
- Request for repeating bioequivalence (BE) study(ies)
- Request for reintegration of chromatograms
- Request for reanalysis of samples
- Request for physicochemical data for ophthalmic products, oral solutions, injections, etc.

- Request for toxicological data

4. Clinical

- The skin irritation, sensitization, and adhesion study for a proposed transdermal product showed that the proposed product was statistically significantly less adhesive than the reference product and/or failed to show that the proposed product is no more irritating than the RLD
- The clinical endpoint BE study did not demonstrate bioequivalence of the test and reference products
- The clinical endpoint BE study is unacceptable due to incorrect endpoint selection and/or study population
- The clinical endpoint BE study did not demonstrate superiority of the test and reference products over placebo
- There is inadequate information provided to ensure the safety of the product in normal clinical use
- There is inadequate information provided to support that the safety of the proposed formulation would not differ from that of the reference product
- The surrogate endpoint (or measurement scale/questionnaire) is not generally recognized as a validated measure for the indication
- The study data are not acceptable due to the concern of data integrity

5. Microbiology

- For terminally sterilized drug products, one or more of the following were not provided or not adequate:
  - Validation of production terminal sterilization process
  - Validation of depyrogenation of product containers and closures
  - Validation of container closure package integrity
- For aseptically filled drug products, one or more of the following were not provided or not adequate:
  - Validation of the sterilizing grade filters (bacterial retention studies)
  - Validation of the sterilization of sterile bulk drug or product contact equipment, components, containers, and closures
  - Validation of the depyrogenation of product containers and closures
  - Validation of the aseptic filling process/line/room (media fills/process simulations)
  - Validation of container-closure package integrity
- For terminally sterilized or aseptically filled drug products
  - Relaxing an acceptance criterion or deleting any part of a specification

APPENDIX B — EXAMPLES OF MINOR AMENDMENTS

1. Type II Drug Master File (DMF)

- Additional stability data needed
- Additional in-process controls needed
- Additional or tightened specifications needed for release or stability
- Method validation or verification report needed

2. Chemistry

- First cycle DMF deficiencies
- Modifications to a validated analytical method to improve performance
- Supporting information needed for qualification of impurity levels, excluding new studies
- Additional or enhanced in-process controls needed for the manufacturing process
- Particle size distributions need to be established for drug substance, excipients and/or granulations
- Additional clarification required for scale-up planning or demonstration of product/process understanding
- Additional information regarding unexpected trends observed during stability studies not linked to formulation or container/closure systems
- Modifications to the container/closure system to increase protection from light, water or oxidation not requiring the submission of additional studies

3. Bioequivalence

- Deficiencies that are not classified as major or ECDs will be classified as minor BE deficiencies

4. Clinical

- Deficiencies that are not classified as major or ECDs will be classified as minor clinical deficiencies

5. Microbiology

- Incomplete or missing information in an existing study that is not classified as major or ECD will be classified as minor microbiology deficiencies

6. Labeling

- Deficiencies that are not classified as major or ECD will be classified as minor

818 labeling deficiencies
819

APPENDIX C — EXAMPLES OF EASILY CORRECTABLE DEFICIENCIES

1. Type II Drug Master File (DMF)

- Missing data points that applicant is likely to have
- Inconsistencies in different sections of the application
- Missing some details in the analytical method

2. Chemistry

- Request for a postapproval commitment (e.g., submission of data acquired during manufacture of the first three commercial batches)
- Missing data points that applicant is likely to have
- Inconsistencies in different sections of the application
- Missing some details in the analytical method

3. Bioequivalence

- Data given in wrong format
- Missing information and data
    - Long-term stability studies
    - Potency assay
    - Formulations
    - Content uniformity
- Deficiencies already identified by the office as ECDs
    - Clarification of data already submitted
    - Request for a postapproval commitment
    - Final resolution of technical issues such as finalization of specifications
- Requests for any of the following:
    - Analytical and/or clinical study reports for failed or pilot studies
    - Analytical run data, chromatograms, etc.
    - Case report forms
    - Analytical/Clinical site information such as addresses
    - Fed meal description
    - Components and composition of certain inks, capsule shells, etc.

4. Clinical

- Any request for clarification (including clarification of statistical tables or assumptions)
- Any missing information (clinical and statistical) that the firm would be able to collect and submit within 10 business days

5. Microbiology

- Clarification on typos or conflicting statements or information
- Misplaced information
- Missing Letters of Authorization (LOAs)

6. Labeling

- Drug product strengths inadequately differentiated on labels and labeling
- Patent/exclusivity expiring before approval of the ANDA requiring the ANDA to update labeling
- Incorrect established name used in the labeling

880 **APPENDIX D — AMENDMENTS FLOW CHART**

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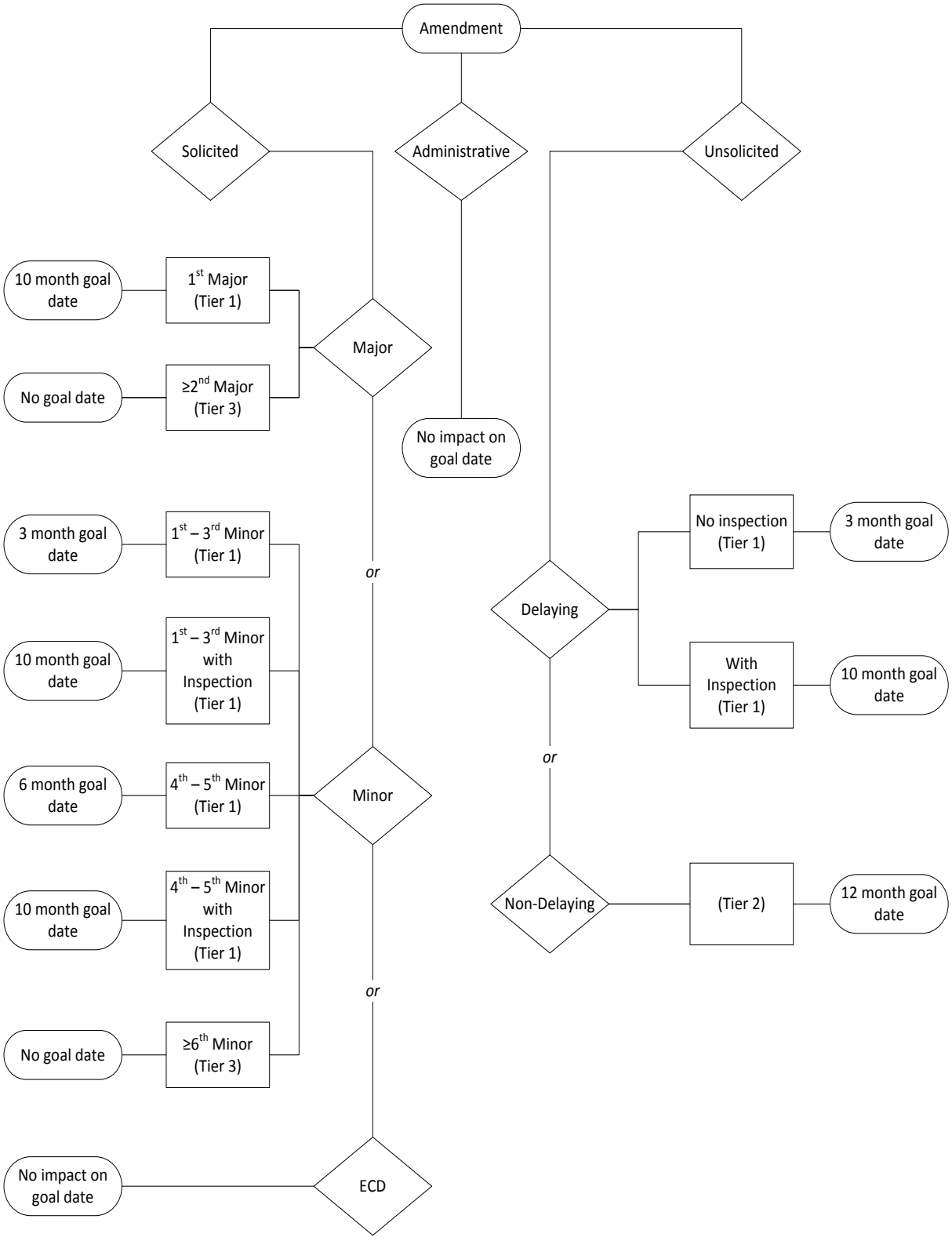

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