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FDA Publishes Industry Guidance Document for Amendments to Abbreviated New Drug Applications

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In July 2018, the United States Food and Drug Administration (FDA) issued a final guidance document titled, "ANDA Submissions - Amendments to Abbreviated New Drug Applications under GDUFA - Guidance for Industry." A guidance document represents the current thinking and recommendations of the FDA, but is not legally binding.

The Guidance Document explains how amendment submissions in response to FDA's assessment[1] of the ANDA, communicated via a Complete Response Letter (CRL), may affect an application's review goal dates (i.e., the time it will take FDA to respond to an ANDA Amendment). In short, amendments to an ANDA will be designated as "standard" or "priority" and classified as "major" or "minor." FDA will assign a goal date depending on the amendment's assigned designation and classification, and other factors discussed in the guidance, such as whether a facility inspection will be required as a result of the content of the amendment or if the ANDA applicant also submits unsolicited amendments to its ANDA.

The guidance applies to ANDAs that are submitted after October 1, 2017.[2] The guidance also applies to prior approval supplements (i.e., supplements submitted to previously approved ANDAs (PASs)) that are submitted after October 1, 2017. Key concepts covered in the guidance include the following:

A. What type of amendment is submitted?

1) ***Major amendments*** – A major amendment is submitted when the content or data provided by an ANDA applicant in response to a deficiency cited by the FDA will require extensive assessment by the agency. Examples of major amendments include:

- Manufacturing a new batch of drug product for any reason
- Performing a new bioequivalence study

[1] FDA now uses the term "assess" instead of "review" in connection with its handling of ANDAs.

[2] While the Guidance Document also discusses the handling of amendments that have been submitted prior to October 1, 2017, the discussion in this document is limited to submissions made after October 1, 2017.

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- Developing new analytical procedures and providing full validation data[3]

2) ***Minor amendments*** – In contrast to a major amendment, a minor amendment are those responses to deficiencies that require less extensive assessment by the FDA. Examples of minor amendments include:

- Minor deficiencies in the Drug Master File
- Incomplete dissolution data
- Labeling deficiencies that have not been adequately addressed

In the CRL that FDA sends the ANDA applicant for which an ANDA Amendment will be filed, the agency will advise whether the amendment response required will be classified as major or minor.

3) ***Unsolicited amendments*** – The ANDA applicant may also submit an amendment that is not prompted by an FDA-noted deficiency. The amendment will be characterized as major or minor depending on the substance of the content in the amendment. FDA can exercise discretion in determining whether to accept or defer an unsolicited amendment during a review cycle.

B. What are the other factors that impact review timing?

1) ***Is the ANDA subject to standard or priority review?***

FDA can grant an ANDA priority review status when there are no more than three approved drug products listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book) and where there are no patents or regulatory exclusivities that can block approval of the ANDA. ANDAs that include patent challenges under the Hatch-Waxman regime may become eligible for priority review if, during the time the ANDA is pending, there are no blocking patents or regulatory exclusivities, there are no applicable stays (i.e., the 30 month litigation stay or a third party's generic exclusivity period) and there are no generic versions of the reference listed drug (the brand drug) that have been brought to market under an approved ANDA. First filer ANDAs under the Hatch-Waxman regime that involve a challenge to the brand's patents can also qualify for priority review. Other conditions for an ANDA being designated for priority review, such as ANDAs related to drug shortages and public health emergencies are provided in the Manual of Policies and Procedures – Center For Drug Evaluation and Research, MAPP 5240, 3 Rev. 4 (November 9, 2017).[4] If the ANDA is not given a priority status, it is subject to standard review.

2) ***Has the ANDA applicant submitted timely and accurate pre-submission facility correspondence (PFC) (i.e., Information regarding the facilities involved in the manufacturing and testing of the ANDA drug)?***

The sites impacted by the PFC include those where the active pharmaceutical ingredient and the finished drug product are manufactured, as well as the sites where bioequivalence studies have been conducted.[5] The ANDA applicant should submit its PFC at least 60 days prior to the submission of its ANDA and confirm that the PFC is accurate at least 60 days prior to the date of submission of each ANDA amendment.

3) ***Will FDA reclassify the submitted amendment from minor to major?***

Even though the FDA may initially indicate on its CRL that the amendment to be submitted will be minor, if, upon review of the content of the response, FDA believes that the submission creates an issue that requires extensive review by the Agency, it can change the designation of the amendment to major. Examples include if the content results in FDA requiring a pre-approval inspection of a site or if a new dosage strength is contained in the amendment.

4) ***Are there any changes to the drug master file (DMF) referenced in the ANDA?***

Any changes that could impact the safety, efficacy, quality or substitutability of the drug product can be considered by FDA as unsolicited amendments and are subject to the timing guidelines in Parts C and D of this memorandum.

[3] Other examples are provided in Appendix A to the Guidance.

[4] https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf

[5] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM563507.pdf

C. Practical recommendations

As a result of this FDA guidance, we recommend that the following recommendations be adopted as part of your regulatory responsibilities:

1. Understand whether your ANDA has been designated as receiving priority or regular review (and, if appropriate, request priority review at the time of submission)
2. Review any Complete Response Letter from the FDA to determine if the amendment will initially be classified as major or minor
3. Avoid submission of unsolicited amendments unless it is believed to be necessary for approval of the ANDA
4. If your ANDA is subject to Hatch-Waxman litigation and is a first filer application, factor in the expected FDA response time in order to achieve a timely tentative approval
5. If your ANDA is subject to Hatch-Waxman litigation, factor in the expected FDA response time in order to satisfy all regulatory review obligations prior to the expiration of any litigation or regulatory stay periods
6. When requesting final approval, do so at least 90 days before the date that final approval is desired and, unless absolutely necessary, do not make any changes to the ANDA, changes in the status of the manufacturing and/or testing facilities' compliance with good manufacturing practices, or add new facilities to the ANDA. If changes are necessary, submit the request for final approval in accordance with the expected FDA goal review guideline to assure a timely final approval
7. Use a standard first page for all ANDA Amendment submissions that addresses the points in Section F

D. Timing guidelines for FDA's response to ANDA Amendments

FDA's goal is to assess and act on 90 percent of the ANDA Amendments in accordance with the following time periods:

1. Major amendments subject to standard review:
   a. If, because of the amendment, there is no pre-approval facility inspection needed: eight months from submission of the ANDA Amendment
   b. If, because of the amendment, there is a pre-approval facility inspection needed: 10 months from submission of the ANDA Amendment
2. Major amendments subject to priority review:
   a. If, because of the amendment, there is no pre-approval facility inspection needed: six months from submission of the ANDA Amendment
   b. If, because of the amendment, there is a pre-approval facility inspection needed AND the PFC has been properly filed, has been properly maintained and contains current and accurate information[6]: eight months from submission of the ANDA Amendment
   c. If, because of the amendment, there is a pre-approval facility inspection needed AND the PFC has not been properly filed and maintained, or the facility information needs to be updated in the amendment with current and accurate information: 10 months from submission of the ANDA Amendment
3. Minor amendments subject to standard or priority review: three months from submission of the ANDA Amendment
4. Unsolicited amendments submitted during a review cycle: FDA will respond by the later of either: (1) the goal date for the original submission or solicited amendment being amended; or (2) The goal date assigned under the review goals for standard and priority review ANDAs
5. Unsolicited amendments submitted between review cycles: FDA will respond by the later of either: (1) the goal date for the subsequently solicited amendments; or (2) the goal date assigned under the review goals for standard or priority review ANDAs

E. Timing guidelines for FDA's response to PASs

FDA's goal is to assess and act on 90 percent of PASs in accordance with the following time periods:

[6] The information contained in the most recent PFC submission is at least 60 days old and no changes were required in the ANDA Amendment.

1. Major amendments subject to standard review:
    a. If, because of the amendment, there is no pre-approval facility inspection needed: six months from submission of the PAS Amendment
    b. If, because of the amendment, there is a pre-approval facility inspection needed: 10 months from submission of the PAS Amendment
2. Major amendments subject to priority review:
    a. If, because of the amendment, there is no pre-approval facility inspection needed: four months from submission of the PAS Amendment
    b. If, because of the amendment, there is a pre-approval facility inspection needed AND the PFC has been properly filed, has been properly maintained and contains current and accurate information:[7] eight months from submission of the PAS Amendment
    c. If, because of the amendment, there is a pre-approval facility inspection needed AND the PFC has not been properly filed and maintained, or the facility information needs to be updated in the amendment with current and accurate information: 10 months from submission of the PAS Amendment
3. Minor amendments subject to standard or priority review: three months from submission of the PAS Amendment
4. Unsolicited amendments submitted during a review cycle: FDA will respond by the later of either: (1) the goal date for the original submission/solicited amendment; or (2) the goal date assigned under the review goals for standard and priority review PASs
5. Unsolicited amendments submitted between review cycles: FDA will respond by the later of either: (1) the goal date for the subsequent solicited amendment; or (2) the goal date assigned under the review goals for standard or priority review PASs

F. Amendments submitted to tentatively approved ANDAs

An ANDA applicant whose ANDA Amendment has been tentatively approved needs to submit a formal request for final approval. The request should be submitted in accordance with the following guidelines:

1. A request for final approval that contains no new data, information, or other changes to the ANDA should be submitted no later than 90 days before the date on which the ANDA applicant wishes to achieve final approval
2. A request for final approval that includes substantive changes to an ANDA, changes in the status of the manufacturing and/or testing facilities' compliance with good manufacturing practices or adds new facilities will be classified as minor or major and the FDA's response time will be determined in accordance with the timing guidelines for ANDA Amendments outlined in Section D
3. An amendment that is made after the ANDA has obtained tentative approval but is not a request for final approval will be treated in accordance with the guidelines for unsolicited amendments[8]

G. What language should be used when submitting ANDA Amendments?

FDA suggests that any amendment be clearly identified as an amendment on the first page of the submission. In addition, the first page of the amendment should include the following information, as appropriate:

- A statement indicating whether the amendment is unsolicited or in response to an assessment from FDA
- The discipline from which the Information Request/ Discipline Review Letter was issued or the disciplines from which the CRL was issued
- The amendment classification (major or minor) as identified by FDA in a CRL
- If unsolicited, the amendment classification proposed by the applicant
- A statement indicating that the application should be designated as priority (including a justification for that designation)

[7] The information contained in the most recent PFC submission is at least 60 days old and no changes were required in the ANDA Amendment.

[8] FDA may elect to extend its response date to such submission if the earliest final approval date will not occur for several years.

- A statement indicating that the applicant is requesting priority review for the amendment (including a justification for that request)
- A statement indicating if and when a PFC was submitted in preparation for the amendment
- A statement indicating if the amendment is addressing a change in the DMF
- A statement indicating whether the amendment contains any manufacturing or facilities changes (i.e., new facilities or changes that are of the type identified on the FDA Form 356h, including changes in responsibilities for facilities already listed in the ANDA)

If your business has any questions concerning the guidance, please contact Andrew Solomon at asolomon@polsinelli.com.

To read the full FDA Guidance document, click here.

Learn more...

For questions regarding this information or to learn more about how it may impact your business, please contact one of the authors, a member of our **Hatch-Waxman Litigation and Opinion** practice, or your Polsinelli attorney.

To learn more about our **Hatch-Waxman Litigation and Opinion** practice, or to contact a member of our **Hatch-Waxman Litigation and Opinion** team, visit
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