Refuse to File: NDA and BLA Submissions to CDER

Guidance for Industry

DRAFT GUIDANCE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)

December 2017
Procedural

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to clarify circumstances under which the FDA's Center for Drug Evaluation and Research (CDER) may refuse to file a new drug application (NDA) or supplemental NDA (21 CFR 314.101(d)) or a biologics license application (BLA) or supplemental BLA (21 CFR 601.2) for a therapeutic biological product regulated by CDER,[2] and to underscore the importance of submitting a complete application to minimize the chance of a refuse-to-file (RTF) action by the FDA. In particular, this guidance focuses on the FDA's policy for refusing to file an NDA under § 314.101(d)(3) when the NDA is incomplete because it does not on its face contain information required under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 314.50.

This guidance does not address scenarios in which an application is incomplete under § 314.50(d)(3) because it does not on its face contain information required under sections 505(j) and 507 of the FD&C Act or 21 CFR 314.94. Other circumstances under which the FDA may refuse to file are described in § 314.101(d)(1), (2), and (4) through (9) and will not be discussed in this guidance.[3] This guidance does not address refusal to file of abbreviated new drug applications (ANDAs),[4] and it does not address refusal to file of an NDA for the regulatory

[1] This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For BLAs, § 601.2(a) states that a BLA "shall not be considered as filed until all pertinent information and data have been received by the Food and Drug Administration."

[3] Specific examples of RTF scenarios also can be found in MAPP 6025.4 *Good Review Practice: Refuse to File* available on the Manual of Policies and Procedures web page at https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

[4] See the guidance for industry *ANDA Submissions — Refuse-to-Receive Standards*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

deficiencies described in § 314.101(e). This guidance is not applicable to BLA submissions for biological products regulated by the Center for Biologics Evaluation and Research.

This guidance also does not discuss the details of the format of an application required by § 314.50 or § 601.2 (NDA or BLA format) nor content required under 21 CFR 54.4(c) (financial disclosure) (see the Appendix). Although missing or inadequate information to address the requirements under section 505(b) of the FD&C Act and § 314.50 can be the basis for refusal to file an NDA discussed in the guidance, the specific format requirements detailed in § 314.50 will not be further described in this guidance. Because administrative filing procedures are well understood, this guidance is limited to consideration of whether an application is incomplete on its face for purposes of refusal to file.[5]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The FDA will file an NDA within 60 days of receipt or inform the applicant of the refusal to file.[6] The FDA generally makes filing determinations for BLAs within the same time frame. Filing an application means that the FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review.[7]

FDA regulations describe the possibility that the FDA will consider an application to be deficient, on its face, in a way that precludes a complete review (see §§ 314.101(d) and 601.2(a)). Specifically, § 314.101(d)(3) provides that the FDA may refuse to file an NDA if:

> "The NDA . . . is incomplete because it does not on its face contain information required under section 505(b) . . . of the Federal Food, Drug, and Cosmetic Act and § 314.50 . . . ."

When this is the case, the FDA may not accept the application for review and may refuse to file it.[8]

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[5] On May 19, 2017, the FDA withdrew its previously published guidance for industry *Refusal to File* (issued July 12, 1993). The FDA is issuing this guidance to update and clarify CDER's procedures for determining whether an application should be refused for filing because it is incomplete on its face. This guidance includes procedures for certain BLAs and supplemental BLAs, given that CDER has regulatory responsibility for certain therapeutic biological products subject to licensing under the Public Health Service Act.

[6] See § 314.101(a).

[7] See § 314.101(a)(1) (regarding NDAs).

[8] See section III.C., Applicant Response, for a description of filing over protest.

Since the early 1990s, the FDA's processes and timelines for reviewing newly submitted applications have substantially evolved. The administrative complexity of applications, with corresponding complexity in determinations of application *completeness*, has increased. For an NDA for a new molecular entity (NME) or an original BLA regulated by CDER, the PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017 established a review model (referred to as *the Program*) to promote greater transparency and to improve communication between the FDA and the applicant during the review of such applications.[9]

When discussing the planned submission of these applications at a presubmission meeting, the FDA and the applicant reach agreements regarding the content of a complete application for the proposed indication(s) as well as agreements, if any, on submission of minor components that may be submitted not later than 30 calendar days after submission of the original application. Unless the applicant and the FDA have agreed at the presubmission meeting to delayed submission of certain components of the application, the FDA expects applications to be complete at the time of submission.[10] If agreed-upon delayed minor components are not received within 30 calendar days after receipt of the original application, the application will be considered incomplete. Incomplete applications may be refused for filing. A *rolling review* permitted under fast track designation has similar obligations.[11]

Documenting agreements reached at presubmission meetings for drug products that are part of the Program, then ensuring that only agreed-upon components are submitted after receipt of the original application and that these agreed-upon components are received within the 30-day window and are complete, has added significant complexity to a determination that an application is *complete*.

The FDA has also committed to timely review of applications under the Prescription Drug User Fee Act. The overall goal is to efficiently and effectively review applications, and thus it is critical to avoid use of resources to review an application when necessary components are so facially deficient as to render them incomplete. The FDA exercises its RTF authority for incomplete applications to optimize the use of both the applicant's and the FDA's resources. RTF actions allow the FDA to notify applicants of application deficiencies as soon as possible, rather than waiting until the end of a review cycle and notifying the applicant in a complete response letter. This process can lead to more rapid approval of safe and effective drug and biological products.

[9] See https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm327030.htm.

[10] See the PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017 (https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm149212.htm).

[11] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

III. PROCESS AND PROCEDURES

A. Filing Review and Assessment

The FDA's initial assessment of a submitted application focuses heavily on assessing the completeness of the application, because incompleteness can lead to refusal to file. Before commencing review of an application, it is important for the FDA to be assured that there will in fact be a complete application that can be reviewed. An application may be considered incomplete for purposes of § 314.101(d)(3) based on deficiencies that on their face render an application incomplete, including applications that are unreviewable or inconsistent with statutory or regulatory requirements.

During the filing review, FDA staff may also identify certain review issues that result in a refusal to file pursuant to § 314.101(d)(3) and other authorities.[12] Review issues typically are not usually considered the basis for an RTF action but are communicated to applicants in official filing correspondence, including RTF letters. However, some review issues may render an application incomplete and may therefore result in a refusal to file.

To make filing determinations, FDA staff assess the completeness of an application and determine the extent and type of deficiencies, if any, by considering the significance of the missing or incomplete information in the context of the proposed drug product, the proposed indication(s), and the amount of time needed to address any given deficiency. Filing issues generally are grouped into two categories as follows:

(1) Potentially easily correctable deficiencies, which applicants typically can correct before filing. This category is not discussed further in this guidance.

(2) Complex significant deficiencies that cannot be corrected before filing and that may result in a refusal to file pursuant to § 314.101(d)(3) and other authorities. Examples of such deficiencies include, but are not limited to:

   (a) Materially lacking or inadequately organized applications that would not permit timely, efficient, and complete review by all relevant review division disciplines as outlined in the guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products*.

   (b) Parts of applications that contain inadequate information for one or more indications when multiple indications are submitted in the same application. The FDA may accept for filing those parts of an application that represent complete submissions for particular indications but refuse to file those parts that are determined to be incomplete for other indications.

   (c) An application that relies on a single adequate and well-controlled trial for a demonstration of effectiveness if prior communication between the FDA and the applicant (i.e., end-of-phase 2 meeting) determined the need for more than one trial to

[12] See MAPP 6025.4 *Good Review Practice: Refuse to File*.

demonstrate effectiveness and if the submitted justification for reliance on a single trial is inadequate. (The FDA may determine that data from a single adequate and well-controlled trial and confirmatory evidence is sufficient to establish effectiveness (see section 505(d) of the FD&C Act); this is further discussed in the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.)

(d) Failure to submit an assessment of studies related to the potential abuse of a drug, necessary to inform drug scheduling under the Controlled Substances Act and the development of drug product labeling. This requirement applies when the drug affects the central nervous system (as determined in animal or human studies), is chemically or pharmacologically similar to other drugs with known abuse potential (such as an opioid, stimulant, depressant, or hallucinogen), or produces psychoactive effects such as euphoria, mood changes, depression, or hallucinations. See § 314.50(d)(5)(vii) and the guidance for industry *Assessment of Abuse Potential of Drugs*.

(e) Required content is not submitted electronically where the FDA has specified the format of such submissions in guidance pursuant to section 745A of the FD&C Act or required content is not submitted in an electronic format that the FDA can review, process, and archive, where such electronic submissions are required by an applicable regulation.[13] Electronic submission issues that CDER considers to be filing issues include particular organization, file format, coding, or formatting problems that are specified in applicable guidances issued pursuant to section 745A(a) of the FD&C Act.[14]

(f) NME NDAs or original BLAs reviewed under the Program, if the minor components agreed upon for late submission at the presubmission meeting are not received within 30 calendar days after receipt of the application.

B. FDA Decision-Making and Notification to the Applicant

After completion of the filing reviews and discussion of the reviews at an internal filing meeting, the division director (or designee) of the relevant review division makes the final filing decision. If the division director (or designee) determines that an application cannot be filed, the review

[13] See, for example, 21 CFR 314.80(g) and the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* as follows: "A submission that is not in the electronic format(s) described in this guidance document will not be filed or received, unless it has been exempted from the electronic submission requirements (see section III.C) with respect to that submission."

[14] For more information about electronic submissions, applicants should refer to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. The FDA also posts detailed information about electronic submissions periodically on the Electronic Submissions Gateway web page at https://www.fda.gov/forindustry/electronicsubmissionsgateway/.

division will communicate an RTF action to the applicant by day 60 in the form of official correspondence.

C. Applicant Response

Within 30 days of the date of the review division's RTF notification, the applicant may request in writing an informal conference with the FDA to discuss whether the FDA should file the application.

In general, the review division will grant an informal conference request if submitted within the 30-day time frame described above.[15] If, after the informal conference, the applicant requests that the review division file the application (with or without amendments to correct the deficiencies), the review division will file the application over protest pursuant to § 314.101(a)(3), notify the applicant in writing, and review it as filed. The applicant need not resubmit a copy of an application filed over protest. If an NDA is filed over protest, the filing date will be designated as 60 days after the receipt date of the informal conference meeting request.[16] Applications for NME NDAs or original BLAs received between October 1, 2012, through September 30, 2017, that are filed over protest will not be reviewed under the Program.[17] Alternatively, the applicant may amend the NDA and resubmit it, and the review division will make a separate determination whether the resubmitted NDA may be filed.[18]

[15] See § 314.101(a)(3) (regarding NDAs). CDER grants informal conference requests submitted within the same time frame for BLAs.

[16] Id.

[17] See the PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017 (https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm149212.htm).

[18] See § 314.101(a)(3).

APPENDIX: SELECT REFUSE-TO-FILE AUTHORITIES

The authorities relevant to refusal to file a new drug application (NDA)[19] or biologics license application (BLA) include, but may not be limited to, the following sections of the Code of Federal Regulations:

- 21 CFR 314.50, content and format of NDAs

- 21 CFR 601.2(a), applications for biologics licenses; procedures for filing

- 21 CFR 54.4(c), financial disclosure requirements

  – The FDA may refuse to file any marketing application that does not contain the information required by this section or a certification by the applicant that the applicant has acted with due diligence to obtain the information but was unable to do so and stating the reason

- 21 CFR 314.101(d)(1) through (9), NDA deficiencies (in relevant part)

  – The NDA does not contain a completed application form (§ 314.101(d)(1))

  – The NDA is not submitted in the form required under § 314.50 (§ 314.101(d)(2))

  – The NDA is incomplete because it does not on its face contain information required under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), § 314.50, or other enumerated provisions (§ 314.101(d)(3))

  – The applicant fails to submit a complete environmental assessment, which addresses each of the items specified in the applicable format under 21 CFR 25.40 or fails to provide sufficient information to establish a categorical exclusion under 21 CFR 25.30 or 21 CFR 25.31 (§ 314.101(d)(4))

  – The NDA does not contain an accurate and complete English translation of each part of the NDA that is not in English (§ 314.101(d)(5))

  – The NDA does not contain a statement for each nonclinical laboratory study that the study was conducted in compliance with the requirements set forth in 21 CFR part 58, or, for each study not conducted in compliance with part 58, a brief statement of the reason for the noncompliance (§ 314.101(d)(6))

  – The NDA does not contain a statement for each clinical study that the study was conducted in compliance with the institutional review board regulations in 21 CFR part 56, or was not subject to those regulations, and that it was conducted in compliance with the informed consent regulations in 21 CFR part 50, or, if the study was subject to but

[19] See also 21 CFR 314.101(e).

was not conducted in compliance with those regulations, the NDA does not contain a brief statement of the reason for the noncompliance (§ 314.101(d)(7))

- The drug product that is the subject of the submission is already covered by an approved NDA or abbreviated new drug application (ANDA) and the applicant of the submission: (1) has an approved NDA or ANDA for the same drug product; or (2) is merely a distributor and/or repackager of the already approved drug product (§ 314.101(d)(8))

- The NDA is submitted as a 505(b)(2) application for a drug product that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the FD&C Act (§ 314.101(d)(9))[20]

[20] The term *duplicate* generally refers to a drug product that is the *same* as a listed drug with respect to active ingredient(s), dosage form, strength, route of administration, and conditions of use, among other characteristics. The FDA intends to consider on a case-by-case basis any assertions by a prospective 505(b)(2) applicant that there is uncertainty about whether a listed drug contains the same active ingredient as the proposed drug product.