POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

Good Review Practice: Refuse To File

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PURPOSE

This MAPP outlines the policies, responsibilities, and procedures for the Office of New Drugs (OND) staff to follow when determining whether there is a basis to refuse to file a new drug application (NDA) or supplemental NDA (under 21 CFR 314.101(d)(1)–(9)), or a biologics license application (BLA) or supplemental BLA (under 21 CFR 601.2)[1] submitted to the Center for Drug Evaluation and Research (CDER).[2]

This MAPP is consistent with existing policies and procedures contained within appropriate sections and resources highlighted in the 21st Century Review process and its

[1] For BLAs, 21 CFR 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." Recognizing that, for both drugs and biologics, a complete application is needed for review and that the data needed to support approval of BLAs and NDAs are in many ways similar, CDER may refuse to file a BLA for a biological product under many of the same conditions as it could to refuse to file an NDA.

[2] For the purposes of this MAPP, the term *application* refers to original BLA submissions and supplements for therapeutic biological products regulated by CDER and to original NDA submissions and supplements.

accompanying Desk Reference Guide,[3] and is intended to provide additional clarification about the refuse-to-file (RTF) process.

This MAPP focuses on CDER's policy for refusing to file an NDA under § 314.101(d)(3) to provide clarity and direction to CDER staff.[4] The regulations in 21 CFR 314.50 or 601.2 (NDA or BLA format) and 314.94 describe the required content of an application that if not contained in the application can lead to an RTF action. This MAPP does not focus on the information called for in those sections, because the need for that information, specified in the regulations, is presumed.

Even if information called for in §§ 314.50 or 601.2 and 314.94 is provided, the FDA will consider its adequacy in the review, and this assessment may lead to *filing review issues*, defined as substantive concerns that may affect conclusions drawn from submitted information and ultimately affect approval of the application;[5] they are separate from application deficiencies that serve as a basis for an RTF action. Review issues are discussed in MAPP 6010.5 *NDAs and BLAs: Filing Review Issues*.

This MAPP is one in a series of MAPPs designed to document good review practices for review staff in accordance with MAPP 6025.1 *Good Review Practices*.

BACKGROUND

RTF is an important regulatory tool to help CDER avoid unnecessary review of incomplete applications or certain applications that are submitted as an NDA but should have been submitted as an abbreviated new drug application (ANDA). Incomplete applications can lead to multiple-cycle reviews and inefficient use of CDER resources. CDER also believes an RTF action can allow an applicant to begin repair of critical deficiencies in the application far sooner than if these were identified much later in a

[3] See MAPP 4180.4 *NDAs/BLAs: Using the 21st Century Review Process Desk Reference Guide* (https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm).

[4] Section 314.101(d)(3) states that the FDA may refuse to file an application if "the NDA or [abbreviated new drug application] ANDA is incomplete because it does not on its face contain information required under section 505(b) or section 505(j), of the Federal Food, Drug, and Cosmetic Act and § 314.50 or § 314.94. In determining whether an ANDA is incomplete on its face, FDA will consider the nature (e.g., major or minor) of the deficiencies, including the number of deficiencies in the ANDA."

[5] Filing review issues are defined as substantive deficiencies or concerns identified by the review team during the initial filing review for an NDA or efficacy supplement that appear to have been inadequately addressed in the application and merit particular attention during the review process. These issues may have significant impact on the FDA's ability to complete the review of the application or approve the application or parts of the application. Filing review issues are distinct from application deficiencies that serve as the basis for an RTF action. Filing review issues pertain only to applications that have been filed.

complete response action and may lead to more rapid approval of safe and effective drug products.

FDA regulations describe the circumstances under which CDER may refuse to file an application. For NDAs, §§ 314.101(d)(1), (2), and (4)–(9) provide many of the reasons for taking an RTF action; CDER considers these reasons to apply to BLAs as well (with the exception of § 314.101(d)(9), which applies only to 505(b)(2) applications).[6] The reasons are listed below and do not require more detailed explanation:[7]

- 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)) (see Attachment 2, section 1)

- 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 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 part 50, or if the study was subject to but 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 and the applicant of the submission: (1) has an approved NDA for the same drug product; or (2) is merely a distributor and/or repackager of the already approved drug product (§ 314.101(d)(8))

[6] See note 1, supra.

[7] The reasons listed reflect the regulatory text pertaining to NDAs only.

- The NDA is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug that is eligible for approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (§ 314.101(d)(9))[8]

Section 314.101(d)(3) allows CDER to refuse to file an NDA if the NDA is incomplete because it does not on its face contain information required under section 505(b) or 505(j) of the FD&C Act and § 314.50 (which address content and format considerations for NDAs). In addition, CDER has interpreted § 314.101(d)(3) to permit it to refuse to file an application when required content is presented in a form that makes it inaccessible.

Resources such as discipline-specific filing checklists and internal processes included in the 21st Century Review process were developed to enable a timely and thorough filing review of applications, to provide consistency in applying our RTF authority, and to enhance documentation of deficiencies for the RTF letter.

The FDA applies a review model (referred to as *the Program*) to the review of new molecular entity (NME) NDAs or original BLAs submitted under section 351(a) or 351(k) of the Public Health Service Act 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 make agreements regarding the content of a complete application for the proposed indication(s) as well as agreements, if any, on submission of certain minor components that may be submitted no later than 30 calendar days after receipt of the original application. Applications are expected to be complete as agreed upon by the FDA and the applicant at the presubmission meeting. Incomplete applications, including applications with minor components not received within 30 calendar days after receipt of the original application, as agreed at the presubmission meeting, will be subject to an RTF decision.

POLICY

The following policy statements emphasize CDER's expectation that applications are to be complete at the time of submission and that a piecemeal approach to building a

[8] The term *duplicate* generally refers to a drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug. For certain complex drug products, it may be unclear whether the drug product proposed in a 505(b)(2) application can be shown to contain the *same* active ingredient as a listed drug, as required for approval under section 505(j) of the FD&C Act. In such cases, CDER may permit the proposed drug product to be submitted through the 505(b)(2) pathway. Questions about whether a proposed drug product differs from a listed drug in a manner that would make it ineligible for approval under section 505(j) of the FD&C Act (for example, because of certain differences in inactive ingredients or an intentionally different pharmacokinetic profile (compare 21 CFR 314.54(b))) should be discussed with the OND Immediate Office, the Office of Pharmaceutical Quality, and the Office of Generic Drugs.

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

complete application through amendments following initial submission is unacceptable. These policies reflect CDER's current approach to RTF assessments and are consistent with the principles that underlie the Program.[10]

- CDER staff will refuse to file:

  – Materially incomplete or inadequately organized applications that would not permit timely, efficient, and complete review by all relevant disciplines as outlined in the draft guidance for industry and review staff *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications*.[11]

  – NME or original 351(a) and 351(k) BLA applications 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.

  – A 505(b)(2) application that is a duplicate of a listed drug approved before receipt of the 505(b)(2) application and is eligible for approval under section 505(j) of the FD&C Act. Approval of a duplicate listed drug during the filing period for the 505(b)(2) application will not preclude filing.

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

  – An application that relies on a single adequate and well-controlled trial to support approval if prior communication between the FDA and the applicant (i.e., end-of-phase 2 meeting) determined the need for more than one trial and if any submitted justification for submission of a single trial is inadequate. Reliance on a single active and well-controlled trial is permitted under law, where there is *confirmatory evidence*,[12] and is further discussed in the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

[10] Ibid.

[11] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[12] Italics added for emphasis only.

- CDER staff will:

  – Use discipline-specific standard filing review templates (where applicable)[13] when conducting the filing review.

  – Communicate potentially easily correctable deficiencies to the applicant with sufficient time for these deficiencies to be corrected before the filing date.

  – Not communicate potentially easily correctable deficiencies if there are other or more complex deficiencies that will lead to an RTF regulatory action.

  – Provide input to the division director, who makes the final filing decision and has signatory authority on RTF letters.

  – Communicate an RTF action to the applicant by day 60 in the form of official correspondence.

  – Arrange for an *informal conference* (as described in § 314.101(a)(3)) if an applicant's written request is submitted within 30 days of the RTF notification.

  – File the application if the applicant: (1) has had an informal conference; and (2) makes the request to file the application over protest. The date of filing for applications filed over protest will be the date 60 days after the date the applicant requested the informal conference (§ 314.101(a)(3)), or a date that is established relative to when the obligation of a user fee has been met. Note that applications for NME NDAs or original biologics received between October 1, 2012, through September 30, 2017, that are filed over protest will not be reviewed under the Program.

RESPONSIBILITIES

Review teams should use materials pertinent to the RTF process from the 21st Century Review web page to conduct an appropriate and complete filing review and to document any application deficiencies that might result in an RTF action. These materials include the filing meeting description and agenda template, discipline-specific filing templates, and pertinent sections of the Desk Reference Guide. Responsibilities are described below.

[13] Review templates are available on the 21st Century Review intranet Web page.

Discipline Primary Reviewers will:

- Conduct an initial assessment of the application, its contents (including summaries), and any responses received to information requests during the filing period to determine the fileability of an application (filing review).

- During the filing review, consider background information about the proposed drug product's development, relevant history of the proposed drug product, the FDA's concerns conveyed to the applicant during the drug product's development, and the applicant's communications to the FDA throughout the drug product development (e.g., when resolving issues identified by the FDA).

- Review the section(s) of the application pertinent to their disciplines and identify any deficiencies that may be a basis for an RTF action. Discuss potential filing issues that may affect multiple disciplines with reviewers from the other disciplines, as appropriate.

- Characterize deficiencies identified during the filing review period as either potentially easily correctable or as more complex deficiencies that are not likely to be easily corrected. Immediately communicate potentially easily correctable RTF deficiencies, along with a suggested deadline for applicant response, to the discipline team leader for concurrence.

- If the discipline team leader concurs, communicate the potentially easily correctable RTF deficiencies with recommended response deadline to the cross-discipline team leader (CDTL) and the OND regulatory project manager. These deficiencies should be forwarded to the applicant as early as possible during the filing period.

- Review the applicant's responses received during the filing period regarding potentially easily correctable RTF deficiencies to determine whether the deficiencies have been resolved to an extent that they are no longer a basis for an RTF action. Communicate this recommendation to the discipline team leader.

- Document the filing recommendation and any RTF deficiencies (including those that were communicated to and corrected by the applicant during the filing review) in a discipline-specific filing review (e.g., completion of discipline-specific filing checklist or other written review). Reviews should distinguish deficiencies that would support an RTF action from other deficiencies (or concerns) that will be communicated to the applicant in the RTF letter but do not form a basis for an RTF action. Discuss with the discipline team leader before the filing meeting.

- Present the discipline review team's conclusions about the fileability of the application at the filing meeting.

- Finalize and archive the discipline-specific filing review.

Discipline Team Leaders, **including the CDTL, will:**

- Determine, upon consultation with the division director, whether potentially easily correctable RTF deficiencies identified by the primary reviewer at any time during the filing period should be conveyed to the applicant (with recommended response deadlines during the filing review).

- Review the discipline primary reviewer's draft discipline filing review.

- Review the discipline primary reviewer's recommendation as to whether an applicant's response to communicated deficiencies was sufficient and share this information with the division director to aid in the RTF action decision-making.

- Determine whether more complex deficiencies identified by the discipline primary reviewer are a potential basis for an RTF action, and whether these deficiencies preclude communication of potentially easily correctable deficiencies.

- Present any differing professional opinions at the filing meeting and, where applicable, document the discipline team leader's (or CDTL's) recommendations in writing.

OND Regulatory Project Managers will:

- Schedule a filing meeting to be held by day 30 for priority reviews and day 45 for standard reviews.

- Determine, in consultation with the Office of Pharmaceutical Quality and/or the Office of Generic Drugs, whether a proposed drug product submitted in a 505(b)(2) application is a duplicate of a listed drug and eligible for approval under section 505(j) of the FD&C Act.

- Communicate potentially easily correctable RTF deficiencies to the applicant, including a deadline for applicant response to these deficiencies. The response deadline should allow sufficient time for review of the applicant's responses before the close of the filing review period (deadline to be determined by the CDTL after consulting with the discipline team leader based on the nature and complexity of such deficiencies). All easily correctable deficiencies from each of the disciplines should be sent to the applicant at the same time, if possible.

- Ensure timely distribution of responses received from the applicant to the review team for review before the filing meeting.

- By day 60, notify the applicant of an RTF decision by letter that describes the basis for the RTF action and distinguishes RTF deficiencies from any other identified concerns or deficiencies that are communicated to the applicant within the letter.

- For applications filed over protest, contact CDER's PDUFA (Prescription Drug User Fee Act) user fee staff to ensure that the applicable user fee clocks have been appropriately adjusted in CDER's data management system.

Division Directors will:

- Attend the filing meeting, review all filing concerns of the review team, and make the final determination about the fileability of an application.

- Inform the office of drug evaluation (ODE) director[14] of when there is disagreement in the RTF recommendations between the division director and that of a discipline supervised by the division director. Dispute resolutions should follow CDER's process as outlined in MAPP 4151.1 Rev.1 *Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain.*

- Inform the ODE director when the division director disagrees with another discipline not supervised by the division director. Differences in scientific opinion should follow CDER's process as outlined in MAPP 4151.8 *Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions*.

PROCEDURES

1. Overview

When conducting a filing review of an application, reviewers should refer to:

- Filing checklist for the relevant discipline.

- Regulations detailing the requirements of an application.

- General or drug class guidance concerning data recommendations for each application section.

[14] For purposes of this MAPP, references to the ODE director include the directors of the Office of Antimicrobial Products and the Office of Hematology and Oncology Products.

- Indication-specific guidance concerning data or trial design recommendations.

- Communications to the applicant during drug product development that conveyed the review division's approval expectations (e.g., documentation from end-of-phase 2 meetings concerning the scope and design of phase 3 pivotal trials; special protocol assessments, documentation from pre-NDA or pre-BLA meetings).

- Approval requirements for relevant previously approved members of a drug's class.

2. Filing Issues

   a. Distinguishing filing issues from review issues

RTF actions should be based only on filing issues, not on review issues. However, many issues do not fit easily into these categories, and often whether an issue is a filing or review issue depends on the magnitude of the deficiency. The distinction is often dependent on review of the application information as well as other factors, as noted below. The following descriptors delineate filing and review issues:

- Filing issues are deficiencies that on their face render an application unreviewable, administratively incomplete, or inconsistent with regulatory requirements. Review of the individual application is important in determining the extent and type of deficiencies, if any, considering the significance of the missing information in the context of the drug product, the proposed indication, and the amount of time needed to address any deficiency. Filing issues may be further subdivided into:

  – Potentially easily correctable deficiencies (see Attachment 1 for examples of these types of deficiencies[15])

  – Complex significant deficiencies that preclude correction before filing (see Attachment 2 for examples of these types of deficiencies)

- Review issues are concerns that require in-depth review and complex judgments. Examples of review issues include, but are not limited to:

  – Risk and benefit assessments

[15] Although a single deficiency on this list may be easily correctable, a combination of these issues may indicate an incomplete application and may be subject to refuse to file.

- Magnitude of drug product effect and its clinical significance

- Reliance on a single adequate and well-controlled trial to support approval if, based on prior discussions with the applicant, the division agreed to accept for filing an application based on a single adequate and well-controlled trial, or if the applicant's justification for reliance on a single trial was found to be acceptable for filing of the application during the filing review

- Acceptability of study endpoints and/or trial design provided that CDER has not previously communicated (e.g., end-of-phase 2 meeting, special protocol assessment (SPA), or indication-specific guidance) that the proposed study endpoints or trial design was not acceptable

- Acceptability of a surrogate endpoint provided that CDER has not previously communicated (e.g., end-of-phase 2 meeting, SPA, or indication-specific guidance) that the proposed surrogate endpoint was not appropriate for disease-specific clinical trials

- Nuances of protocol design

- Adequacy of statistical plans and analyses (e.g., adjustments for multiple endpoints, choice of an appropriate noninferiority margin, how missing data were handled) provided that CDER has not previously communicated (e.g., end-of-phase 2 meeting, SPA, or indication-specific guidance) that the planned statistical analyses were not appropriate

- Adequacy of the pediatric assessment, as required by the Pediatric Research Equity Act of 2007 (PREA)[16]

b. Electronic submissions: Document, format, technical, and quality issues

These issues include particular organization, file format, coding, or formatting problems that render the application unreviewable. During the filing review, reviewers should attempt to open datasets in a software program such as Adobe Acrobat, SAS, or JMP to examine them. An applicant's failure to submit a section that is reviewable is functionally equivalent to omission of the section (e.g., failure to provide data in a format specified by the FDA) and thus a basis to refuse to file (see section 1 in Attachment 2).

The requirements to ensure accessibility of all necessary data, including subject-level data tabulations in electronic form if submitted, efficacy analysis datasets, and subject-

[16] Section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355c), as amended by PREA, Title IV of the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85, 121 Stat. 823).

level safety files, in electronic submissions, should be determined based on relevant guidance (e.g., the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*). CDER's Office of Business Informatics should be consulted before an application is refused filing on the basis of electronic inaccessibility.

If the application does not comply with the electronic format for submission provisions of section 745A of the FD&C Act[17] or other relevant guidance regarding electronic submissions, CDER may choose to refuse to file the application.

3. Addressing Potentially Easily Correctable RTF Deficiencies

   a. Minor deficiencies that can be corrected by the applicant in time to allow adequate CDER assessment of the completeness of the application before the filing date and that do not substantially affect the ability of the review team to begin its substantive review should be conveyed to the applicant as early in the filing review period as possible, preferably before the filing meeting.

      - Given the tight time frame for addressing these deficiencies, discipline primary reviewers should discuss such deficiencies shortly after identifying them with their discipline team leader. The discipline team leader, in turn, should discuss with the CDTL to determine quickly whether communication to the applicant is supported by the division director.

      - These filing issues may be conveyed by telephone conference, facsimile, secure email, or other expedient means of communication. Although a review division can offer an applicant the chance to correct such deficiencies, the review division is not obligated to review the newly submitted information if insufficient time remains within the filing review period. The RTF decision cannot be delayed beyond the filing date.

   b. An RTF action should be issued for applications in which potentially easily correctable RTF deficiencies are too numerous to be corrected by the applicant before the filing date. The applicant need not be given an opportunity to correct numerous RTF deficiencies.

   c. Deficiencies that are not addressed by the applicant:

      - If the applicant is given the opportunity to correct an RTF deficiency and the response provided to CDER within the specified time frame is not adequate, the review team should refuse to file the application because further delay compromises the ability of the review team to comply with good review

[17] See section 1136 of the Food and Drug Administration Safety and Innovation Act.

management practices and does not guarantee satisfactory correction of the deficiency.

- Examples of significant deficiencies that preclude review and that are not easily correctable are included in Attachment 2.

4. Decision-Making at the End of the Filing Review Period

- After completion of the filing reviews for a marketing application, the division director should make one of the following two decisions:

    1. File the application: If the application is complete for review, the application will be filed.

    2. Refuse to file the application: If the application is incomplete, the potentially correctable deficiencies cannot be readily rectified or have not been rectified, or the application is inconsistent with regulatory practice (i.e., a 505(b)(2) application is submitted that could have been a 505(j)), CDER will refuse to file the application.

- The OND review division will communicate the deficiencies to the applicant so that they may be corrected in a resubmission.

REFERENCES[18]

1. 21 CFR 314.50, content and format of NDAs

2. 21 CFR 314.101, Filing an application and receiving an abbreviated new drug application

3. 21 CFR 54.4(c), financial disclosure requirements[19]

4. 21 CFR 601.2, Applications for biologics licenses; procedures for filing

[18] MAPPs can be found at https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm and guidances for industry can be found at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[19] 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.

5. MAPP 4151.1 Rev. 1 *Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain*

6. MAPP 4151.8 *Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions*

7. MAPP 4180.4 *NDAs/BLAs: Using the 21st Century Review Process Desk Reference Guide*

8. MAPP 6010.5 *NDAs and BLAs: Filing Review Issues*

9. MAPP 6025.1 *Good Review Practices*

10. Guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements*

11. Guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*

12. Guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*

13. Guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products*

14. CDER 21st Century Review Process Desk Reference Guide located on the 21st Century Review intranet web page

15. Study Data Specifications Document at https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

16. PDUFA Reauthorization Goals and Procedures Fiscal Years 2018 Through 2022 https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf

17. Biosimilar Biological Product Authorization Performance Goals and Procedures for Fiscal Years 2018 Through 2022 https://www.fda.gov/downloads/forindustry/userfees/biosimilaruserfeeactbsufa/ucm521121.pdf

EFFECTIVE DATE

This MAPP is effective upon date of publication.

ATTACHMENT 1: EXAMPLES OF POTENTIALLY EASILY CORRECTABLE DEFICIENCIES

In isolation, the list below provides examples of potentially easily correctable deficiencies. But as previously noted, although a single deficiency on this list may be easily correctable, a combination of these issues may indicate an incomplete application and may be subject to refuse to file.

- Electronic navigational problems
- Electronic compatibility/readability with the FDA's system
- Missing right of reference to information required for an application
- Incomplete or missing Form FDA 356h (Application to Market a New or Abbreviated New Drug or Biologic for Human Use)
- Missing financial disclosure statement on Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and/or Form FDA 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators)
- Incorrectly worded Debarment Certification statement
- Small amounts of missing data (e.g., collected but not submitted)
- Failure to submit the content of labeling in electronic structured product labeling format as described in 21 CFR 314.50(l)(1)(i) for NDAs and supplements and 21 CFR 601.14(b) for BLAs and supplements

ATTACHMENT 2: EXAMPLES OF COMPLEX AND SIGNIFICANT DEFICIENCIES THAT MAY PROVIDE SUPPORT FOR AN RTF ACTION

The following lists provide categories, with accompanying examples of filing deficiencies that, when existing alone (e.g., lack of any adequate and well-controlled trials to support approval) or, more commonly, existing in combination or in combination with deficiencies from Attachment 1, may be used to support an RTF decision. The determination of when to refuse to file an application for such deficiencies will require the judgment of the division director.

1. Missing section(s) of an application that are required by regulation.

The following list, which is not all-inclusive, identifies sections of an application that are required by regulation. Omission of an entire section or sections renders the application incomplete.

- Index and table of contents (§ 314.50(b))
- Summary of the application (§ 314.50(c))
- Chemistry, manufacturing, and controls (§ 314.50(d)(1))
- Nonclinical pharmacology and toxicology (§ 314.50(d)(2))
- Human pharmacokinetics and bioavailability (§ 314.50(d)(3))
- Microbiology, if the drug is anti-infective (§ 314.50(d)(4))
- Clinical data (§ 314.50(d)(5))
- Integrated summary of effectiveness (§ 314.50(d)(5)(v))
- Integrated summary of safety (§ 314.50(d)(5)(vi))
- Statistical evaluation (§ 314.50(d)(6))
- Pediatric use (§ 314.50(d)(7))
- Required case report forms (CRFs) and tabulations (§ 314.50(f))
- Annotated package insert and the marketing history of the drug product outside the United States (§ 314.50(c)(2))
- Complete information on manufacturing and testing facilities and specific activities at each (§ 314.50(d)(1))

- Abuse liability section if the application is one for which this section is required including a proposal for scheduling under the Controlled Substances Act (§ 314.50(d)(5)(vii))

- Integrated summary of the benefits and risks of the drug product (§ 314.50(d)(5)(viii))

- Failure to submit the content and format of labeling as described in 21 CFR 201.56 and 201.57 (Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products) or in the physician labeling rule format (see the guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements*)

- Failure to provide patent certification or statement as described under § 314.54(a)(1)(vi) for a 505(b)(2) application relying on one or more listed drugs

2. Application has all required sections, but some or all sections are incomplete or unable to be reviewed.

This list of examples, which is not all-inclusive, provides examples of inadequate content, presentation, or organization within the required technical sections and integrated summaries that would render a section incomplete. In some cases, the applicant may provide explanations for why a section is not needed or why a particular study/trial could be conducted after approval. The merits of such explanations should be considered as part of the filing review; the mere presence of an explanation is not adequate to support accepting an incomplete application.

a. General

- Application is unreasonably disorganized

- Data tabulations (line listings) and/or graphical displays are not interpretable, are inadequately labeled, or do not indicate the sources of the data

- Inadequate annotation in final reports or summaries of where individual studies/clinical trials or individual data and records can be found

- Problems with hypertext links

b. Clinical/Statistical

- Absence of clinical trial protocols, including amendments to the clinical trial design or statistical analysis plan

- Omission of critical statistical analyses without adequate justification and explanation, such as an analysis accounting for all clinical trial subjects or the protocol-defined primary statistical analysis or analyses

- Absence of randomization information such as: treatment allocation by site, day, and time; randomization scheme; and randomization ratio

- For a 505(b)(2) application, absence of literature or listed drug citation to support the safety/efficacy of the drug product

- Absence of data necessary to support any aspects of the proposed drug product in a 505(b)(2) application that represents modifications to the listed drug(s) relied upon

- Failure to address requirements under PREA because of incomplete or inadequate pediatric assessment, or failure to include an agreed initial pediatric study plan.

c. Quality

- Failure to provide adequate information that assures identity, strength, purity, and quality of the drug substance or drug product (including missing environmental assessment information and/or no drug product or drug substance manufacturer listed)

- Failure to provide the name and address of all facilities involved in the manufacturing process (e.g., drug substance and drug product, control and testing labs, primary packaging and labeling)

- Failure to register all manufacturing sites intended for production of the to-be-marketed drug product

- Failure of facilities referenced in the application to be prepared for inspection upon submission of a new marketing application

- Failure to specify the complete responsibilities of each facility, including activities to support application approval (e.g., produced pilot batch, did stability testing for submission batches) as well as failure to provide a full description of the after approval function(s)

- Stability overages in excess of labeled claim
- Impurities are not characterized or the necessary toxicology studies were not conducted to address them
- Stability data do not support a commercially viable expiration dating period
- Solid dosage form does not contain required code imprint

d. Pharmacology/Toxicology

- Failure to provide necessary pharmacology/toxicology studies (e.g., animal carcinogenicity studies for a drug product intended to be administered chronically, reproductive toxicology studies for a drug product intended for use in people of reproductive age) without an adequate explanation of why the studies are not necessary
- International Conference on Harmonisation limits on impurities exceeded without accompanying animal studies to evaluate the safety of these impurities

e. Clinical pharmacology

- Absence of a bridge (e.g., via comparative bioavailability data) between the proposed drug product and the reference drug product to demonstrate that such reliance is scientifically justified in a 505(b)(2) application
- Use of an unapproved drug as a reference drug product for a bioequivalence study in a 505(b)(2) submission
- Failure to provide bioequivalence data comparing the to-be-marketed drug product with the drug product used in the pivotal clinical trials (e.g., incomplete bridging trials that do not support the marketed formulation)
- Failure to provide bioanalytical method validation and trial-specific bioanalytical method performance information for the bioanalytical assays used to determine drug concentrations in biological matrices
- Failure to provide bioavailability data or a request for biowaiver
- Failure to provide drug disposition information
- Failure to provide drug-drug interaction information

3. Failure to include evidence of effectiveness compatible with statute and regulations. Examples include, but are not limited to:

    - Lack of any adequate and well-controlled investigations/trials (or for 505(b)(2) applications, lack of appropriate supportive literature or citation of reliance of a listed drug), as required by law, including use of obviously inappropriate or clinically irrelevant endpoints

    - Presentation of a single adequate and well-controlled trial without adequate justification of why the single trial should be regarded as fulfilling the statutory requirement for substantial evidence of effectiveness[20]

    - Use of a trial design that is inappropriate (as reflected in regulations or well-established FDA interpretation) for the particular claim

    - Reliance solely on trials that fail to achieve statistical significance on the primary endpoint or endpoints, without an adequate explanation of why this approach is reasonable

    - Reliance on clinical trials with an endpoint that does not constitute clinical benefit and is not a surrogate or intermediate clinical endpoint that is reasonably likely to predict clinical benefit (under 21 CFR part 314, subpart H and under part 601, subpart E), without an adequate explanation and supporting data of why the surrogate or intermediate clinical endpoint should be considered reasonably likely to predict clinical benefit

    - Failure to present a reasonable distribution strategy for a drug product shown to be effective but that can only be safely used if distribution or use is restricted (21 CFR 314.520)

    - Reliance on a trial design that is unethical or uninterpretable (e.g., use of a noninferiority design without any explanation of the choice of noninferiority margin)

    - For a combination drug product, failure to present studies/clinical trials that assess the contribution of each component, without an adequate explanation and supporting data of why the requirement should be waived

    - Absence of the demographic subset analyses specified in the regulations (§ 314.50(d)(5)(V) and (VI))

[20] See guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.*

- Use of a statistical analysis plan that was finalized after data unblinding, raising integrity concerns, without a compelling explanation of why this should be considered reasonable

4. Adequate and well-controlled trials submitted, but content of application is deficient in other aspects, resulting in omission of critical data, information, or analyses needed to evaluate effectiveness and safety or provide adequate directions for use. Examples include:

    - Inadequate collection of critical safety and/or effectiveness data during the conduct of the trial(s) that is needed for the evaluation of safety and/or efficacy as appropriate to the drug class in guidance or well-recognized established practices

    - Inadequate evaluation of the safety and/or effectiveness in the population intended to use the drug product, including pertinent subsets, such as sex, age, and racial subsets, without adequate explanation of why this evaluation is not critical

    - Failure to provide safety data adequate for proposed use at relevant doses (e.g., inadequate long-term exposure safety assessments for chronically administered therapies; inadequate exposure at higher doses)

    - Inadequate exposure data for the target demographic at the appropriate doses and durations, without adequate explanation

    - Absence of an analysis of data supporting the proposed dose and dose interval

    - Omission of protocol amendment summaries and when they occurred in reference to data locks and trial analyses

    - Outcome assessment (e.g., patient-reported outcome tool) not validated in the context of the trials submitted, without adequate explanation of why it should be considered informative

    - For nonprescription monograph ingredients, drug product does not meet the deviation from the monograph standards for the reference monograph and meets the definition of a monograph product

    - A 505(b)(2) application that relies on a proposed or tentative final nonprescription monograph rather than on a final monograph

    - Failure to include required class risk evaluation and mitigation strategy at submission

5. Electronic dataset, technical, and quality issues.

Reviewers should assess datasets for appropriate organization, formatting, and general coding inaccuracies, including inconsistencies between electronic datasets and CRFs with respect to adverse event categories and data presentations. Other examples of general problems with datasets or electronic data within an application include:

- Absence of important variables (e.g., treatment code) on the analysis files containing the primary efficacy data
- Lack of a unique subject ID for each subject throughout for the entire submission
- Files not adequately defined or properly indexed
- Incompatible structures (e.g., different formats for subject ID variables) that prevent merging of datasets
- Data files too large resulting in excessive time to open using common statistical applications such as SAS or JMP
- Missing datasets (the submission must include both the case report tabulation datasets and appropriate analysis files)
- Datasets contain transcription, transposition, or other errors, preventing an independent data review and reducing confidence in the accuracy of the captured data
- Missing key components of datasets such as:
  - Define.pdf or define.xml
  - List of codes used in a database
  - Graphs or other displays that do not reference the data source
  - Not providing definitions of acronyms and/or abbreviations
  - Not using a common MedDRA dictionary
  - Not using a concomitant drug dictionary
  - Scanned CRFs that are illegible