POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

Good Review Practice: Refuse To File

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PURPOSE

- This Manual of Policies and Procedures (MAPP) outlines the policies, responsibilities, and procedures for the Center for Drug Evaluation and Research (CDER) staff to follow when determining whether there is a basis to refuse to file (RTF) 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) submitted to CDER. [1, 2]

- This MAPP is consistent with information contained in the draft guidance for industry *Refuse to File: NDA and BLA Submissions to CDER* (December 2017) and existing policies and procedures, and is intended to provide additional clarification about the

[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 RTF a BLA under many of the same conditions as it could to RTF 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.

RTF processes to CDER staff.[3]

- This MAPP focuses on CDER's policy for refusing to file an NDA under 21 CFR 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 required under 21 CFR 314.50 or 601.2 and 314.94 is provided, the FDA will consider its adequacy in the review. The filing assessment may lead to identification of **filing review issues**, defined as substantive concerns that will likely affect conclusions drawn from submitted information and ultimately affect approval of the application; they are separate issues from application deficiencies that serve as a basis for an RTF action.[5] Review issues are discussed in MAPP 6010.5 *NDAs and BLAs: Filing Review Issues*.[6]

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. In some cases, deficiencies may be easily correctable (see Appendix A for examples) and not require an RTF action. However, in other cases the deficiencies may be more complex and significant (see examples in Appendix B) and CDER 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] For the most recent version of a guidance, refer to the *Search for FDA Guidance Documents* web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] Section 314.101(d)(3) states that the FDA may RTF 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/BLA 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.

[6] For the most recent version of a MAPP, refer to the *CDER Manual of Policies & Procedures* web page at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp.

complete response action. Thus, an RTF action may overall lead to approval of safe and effective drug products in a shorter period of time, avoiding multiple review cycles.[7]

- FDA regulations describe the circumstances under which CDER may RTF an application. For NDAs, 21 CFR 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 21 CFR 314.101(d)(9), which applies only to 505(b)(2) applications). The reasons are listed below and do not require more detailed explanation:[8]

  - The NDA does not contain a completed application form (21 CFR 314.101(d)(1)).

  - The NDA is not submitted in the form required under 21 CFR 314.50 (21 CFR 314.101(d)(2)) (see Appendix B, 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 (21 CFR 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 (21 CFR 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 (21 CFR 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

[7] For the purposes of this MAPP, all references to "drug products" include both human drugs and therapeutic biological products regulated by CDER.
[8] The reasons listed reflect the regulatory text pertaining to NDAs only.

already approved drug product (21 CFR 314.101(d)(8)).

– 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) (21 CFR 314.101(d)(9)).[9]

- 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.

- As part of the 21st Century Review process, CDER developed resources, including discipline-specific filing checklists, to assist reviewers during the filing review of an application. These checklists are tools to help provide consistency in applying our RTF authorities and to enhance documentation of deficiencies for the RTF letter. As part of the filing review, FDA comprehensively considers all relevant information to determine whether an application can be filed in accordance with applicable legal and scientific standards. Samples of the discipline-specific checklists are provided in Appendix C for educational purposes only.

- 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.[10] When discussing the planned submission of these applications at a presubmission meeting, the FDA and the applicant may make agreements regarding certain 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. Unless the applicant and the FDA have agreed at the presubmission meeting to delayed submission of certain components of the application, the FDA expects

[9] 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. Refer to the guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* for additional information on determining the appropriate abbreviated 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.

[10] Refer to the *Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs* at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/program-enhanced-review-transparency-and-communication-nme-ndas-and-original-blas.

applications to be complete at the time of submission. 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 emphasizes CDER's expectation that applications are to be complete at the time of submission and that a piecemeal approach to building a 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.[11]

- **CDER staff will RTF:**

  — 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*.[12]

  – 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 clinical investigation to support approval if prior communication between the FDA and

[11] Ibid.

[12] For the most recent version of a guidance, refer to the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

the applicant (e.g., end-of-phase 2 meeting) determined the need for more than one clinical investigation and if any submitted justification for submission of a single clinical investigation is inadequate.[13]

- **CDER staff will:**

  - Use discipline-specific standard filing review templates[14] (where applicable) 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, in advance of an RTF, if there are other or more complex deficiencies that will lead to an RTF regulatory action.

  - Provide input to the clinical division director or designated signatory authority, who is authorized to make the final filing decision.

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

  - Arrange for an *informal conference* (as described in 21 CFR 314.101(a)(3)) if an applicant submits a Type A meeting request[15] 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 (21 CFR 314.101(a)(3)), or a date that is established relative to when the obligation of a user fee has been met.[16] Note that applications for NME NDAs or original biologics that are filed over protest are

[13] Refer to the draft guidances for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023) and *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019), and the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998). Ibid.

[14] See Appendix C.

[15] See FDA guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*. For the most recent version of a guidance, refer to the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents

[16] Contact the user fee management staff to determine the date the user fee obligation has been met for applications filed over protest.

not eligible for certain parameters of the Program.[17]

RESPONSIBILITIES

Review teams should use materials pertinent to the RTF process 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, and discipline-specific filing checklists. Responsibilities undertaken during the filing period are described below.

- **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).

  – 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 as either potentially easily correctable or as more complex that are not likely to be easily corrected during the filing period.

  – 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.

[17] Refer to the current version of the PDUFA commitment letter found under the *Reauthorization Activities* section on the FDA *Prescription Drug User Fee Amendments* webpage at https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments#68d52a964f74a.

- 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 prior to the filing date.

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

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

  - Determine, upon consultation with the division director, whether more complex deficiencies identified by the discipline primary reviewer are a potential basis for an RTF action and whether potentially easily correctable deficiencies should therefore be included in an RTF letter and not communicated to the applicant during the filing period.
  - 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.

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

- **OND Clinical 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 OND Clinical Office Director of any disagreements in the RTF recommendations. Differences in scientific opinion should follow CDER's process as outlined in MAPP 4151.8 *Equal Voice: Collaboration and Regulatory Policy Decision-Making in CDER*.

PROCEDURES

1. Overview

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

a. The filing checklist for the relevant discipline (see Appendix C).

b. Regulations detailing the requirements of an application.

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

d. Indication-specific guidance concerning data or clinical investigational design recommendations.

e. Communications to the applicant during drug product development that conveyed the review division's 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, advice regarding consumer studies for nonprescription drug products).

f. 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 help delineate filing and review issues:

i. 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:

1. Potentially easily correctable deficiencies (see Appendix A for examples of these types of deficiencies).[18]

2. Complex significant deficiencies that preclude correction before filing (see Appendix B for examples of these types of deficiencies).

ii. Review issues are concerns that require in-depth review and complex

[18] 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 an RTF action.

judgments. Examples of review issues include, but are not limited to:

1. Risk and benefit assessments.

2. Magnitude of drug product effect and its clinical significance.

3. Reliance on a single adequate and well-controlled trial to support approval if, based on prior discussions with the applicant, the OND Clinical review 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.

4. 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 unacceptable.

5. 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 investigations.

6. 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.

7. Adequacy of the pediatric assessment, as required by the Pediatric Research Equity Act (PREA).[19]

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

i. 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 RTF (see section 1 in Appendix B).

[19] Refer to 21 CFR 314.101, sections 505B(a) and 505B(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355c(a), and 21 U.S.C. 355c(e)).

ii. The requirements to ensure accessibility of all necessary data, including subject-level data tabulations in electronic form if submitted, efficacy analysis datasets, and subject-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*). The Office of Business Informatics should be consulted before an application is refused filing on the basis of electronic inaccessibility.

iii. If the application does not comply with the electronic format for submission provisions of section 745A of the FD&C Actor other relevant guidance regarding electronic submissions, CDER may choose to RTF 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.

i. 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.

ii. 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:

i. 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 RTF the application because further delay compromises the ability of the review team to comply with good review management practices and does not guarantee satisfactory correction of the deficiency.

ii. Examples of significant deficiencies that preclude review and that are not easily correctable are included in Appendix B.

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

a. 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. RTF 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 (e.g., a 505(b)(2) application is received that should have been submitted as a 505(j) application), CDER will RTF the application.

b. If the decision is to RTF, OND will communicate the deficiencies to the applicant in an RTF letter so that they may be corrected in a resubmission.

REFERENCES

1. 21 CFR 54.4(c), Financial disclosure requirements[20]

2. 21 CFR 314.50, Content and format of an NDA

3. 21 CFR 314.101, Filing an NDA and receiving an ANDA

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

5. Draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023)

[20] 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.

6. Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)

7. Guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (September 2024)

8. Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

9. Guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019)

10. Draft guidance for industry and review staff *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications* (September 2018)

11. Draft guidance for industry *Refuse to File: NDA and BLA Submissions to CDER* (December 2017)

12. Guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements* (February 2013)

13. Draft guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products* (April 2005)

14. Guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)

15. MAPP 4151.8 *Equal Voice: Collaboration and Regulatory and Policy Decision-Making in CDER*

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

17. Study Data Specifications Document, available from *Study Data Standards Resources* at https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources

18. *Prescription Drug User Fee Amendments*, available at https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments.

19. *Biosimilar User Fee Amendments*, available at https://www.fda.gov/industry/fda-user-fee-programs/biosimilar-user-fee-amendments

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EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
10/11/13	N/A	
09/05/18	N/A	Recertified with no changes.
10/23/25	1	Revised to include checklists that are used internally by FDA to determine if a submitted application is complete and reviewable.

APPENDIX A: 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 deficiencies 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 unsubmitted information (e.g., collect 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

APPENDIX B: 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 clinical investigations to support approval) or, more commonly, existing in combination or in combination with deficiencies from Appendix A, 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.

- 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 (21 CFR 314.50(b))

  – Summary of the application (21 CFR 314.50(c))

  – Chemistry, manufacturing, and controls (21 CFR 314.50(d)(1))

  – Nonclinical pharmacology and toxicology (21 CFR 314.50(d)(2))

  – Human pharmacokinetics and bioavailability (21 CFR 314.50(d)(3))

  – Microbiology, if the drug is anti-infective (21 CFR 314.50(d)(4))

  – Clinical data (21 CFR 314.50(d)(5))

  – Integrated summary of effectiveness (21 CFR 314.50(d)(5)(v))

  – Integrated summary of safety (21 CFR 314.50(d)(5)(vi))

  – Statistical evaluation (21 CFR 314.50(d)(6))

  – Pediatric use (21CFR 314.50(d)(7))

  – Required case report forms (CRFs) and tabulations (21 CFR 314.50(f))

  – Annotated labeling and a brief description of the marketing history, if any, of the drug product outside the United States (21 CFR 314.50(c)(2))

  – Complete information on manufacturing and testing facilities and specific

activities at each (21 CFR 314.50(d)(1))

- Abuse potential section if the application is one for which this section is required including a proposal for scheduling under the Controlled Substances Act (21 CFR 314.50(d)(5)(vii))

- Integrated summary of the benefits and risks of the drug product (21CFR 314.50(d)(5)(viii))

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

- The standardized content and format for the labeling of nonprescription drug products as described in 21 CFR 201.66

- Failure to provide patent certification or statement as described under 21 CFR 314.54(a)(1)(vi) for a 505(b)(2) application relying on one or more listed drugs

- 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.

  - 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 investigations or individual data and records can be found

    - Problems with hypertext links

- Clinical/Statistical

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

  - Omission of critical statistical analyses without adequate justification and explanation, such as an analysis accounting for all clinical investigation 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 an incomplete or inadequate pediatric assessment, or report from a molecularly targeted pediatric cancer investigation, or failure to obtain an agreed initial pediatric study plan prior to the submission of the marketing application[21]

- 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

[21] Inadequacy of the pediatric assessment or report from a molecularly targeted pediatric cancer investigation can be considered either a filing review issue or a filing issue, depending upon the scope of the inadequacy.

- 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 post 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

– 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 non-clinical studies to evaluate the safety of these impurities

– Clinical pharmacology

- Absence of a bridge (e.g., via comparative bioavailability data) between the proposed drug product and the relied-upon listed drug(s) to demonstrate that such reliance is scientifically justified in a 505(b)(2) application

- Use of an unapproved drug as a reference product for a comparative bioavailability/bioequivalence bridging study in a 505(b)(2) application

- Failure to provide bioequivalence data comparing the to-be-marketed drug product with the drug product used in the pivotal clinical investigations (e.g., incomplete bridging studies that do not support the marketed formulation)

- Failure to provide bioanalytical method validation and study-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

- 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 clinical investigations (or for 505(b)(2) applications, lack of appropriate literature or identification of reliance on a listed drug), as required by law, including use of obviously inappropriate or clinically irrelevant endpoints
  - Presentation of a single adequate and well-controlled clinical investigation without adequate justification of why the single clinical investigation should be regarded as fulfilling the statutory requirement for substantial evidence of effectiveness[22]
  - Use of a clinical investigation design that is inappropriate (as reflected in regulations or well- established FDA interpretation) for the particular claim
  - Reliance solely on clinical investigations 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 investigations s 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
  - Reliance on a clinical investigation l design that is unethical or uninterpretable (e.g., use of a noninferiority design without any explanation of the choice of noninferiority margin)

[22] Refer to the draft guidances for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023) and *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019), and the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998)*.

- For a fixed-combination drug product, failure to present studies/clinical investigations 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 (21 CFR 314.50(d)(5)(V) and (VI))

- 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

- Adequate and well-controlled clinical investigations 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 clinical investigation(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)

  - Failure to present a reasonable distribution strategy for a drug product that can only be safely used if distribution or use is restricted under a REMS with Elements to Assure Safe Use (ETASU), if the necessity for such is either apparent (e.g., the drug product is part of a class for which an ETASU REMS is already in place) or was communicated in advance by the review division

  - Inadequate exposure data for the target population 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 clinical investigation analyses

  - Outcome assessment (e.g., patient-reported outcome tool) not validated in the

context of the clinical investigations submitted, without adequate explanation of why it should be considered informative

- For approval of a nonprescription drug product under the NDA deviation process, failure to show that the drug product complies with the conditions of the OTC monograph except for the deviation, or failure to provide the necessary data to demonstrate the safety and effectiveness of the drug product with the deviation (21 CFR 330.11)

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

- Failure to include a required class risk evaluation and mitigation strategy at the time of submission

- 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

APPENDIX C: DISCIPLINE FILING CHECKLISTS

CLINICAL FILING CHECKLIST

IMPORTANT: This checklist is a sample of a tool used to assist reviewers during the filing review of an application. All decisions regarding whether an application can be filed are based on a comprehensive review of all relevant information in accordance with applicable legal and scientific standards.

Content Parameter		Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).				
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?				
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?				
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?				
5.	Are all documents submitted in English or are English translations provided when necessary?				
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances.				
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?				
8.	Has the applicant submitted the integrated summary of safety (ISS)?				
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?				
10.	Has the applicant submitted a benefit-risk analysis for the product?				
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				

	Content Parameter	Yes	No	N/A	Comment
12.	If appropriate, what is the relied upon listed drug(s)?				
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?				
14.	Describe the scientific bridge (e.g., BA/BE studies)				
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms: Location in submission:				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:				
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?				
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.				

Content Parameter		Yes	No	N/A	Comment
SAFETY					
19.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?				
20.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (e.g., QT interval studies, if needed)?				
21.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?				
22.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure)[23] been exposed at the dosage (or dosage range) believed to be efficacious?				
23.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?				
24.	Has the applicant submitted the coding dictionary[24] used for mapping investigator verbatim terms to preferred terms?				
25.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?				
26.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?				

[23] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[24] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	N/A	Comment
OTHER STUDIES					
27	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?				
28	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?				
PEDIATRIC USE					
29	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?				
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
30	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-resources)?				
ABUSE LIABILITY					
31	If relevant, has the applicant submitted information to assess the abuse liability of the product?				
FOREIGN STUDIES					
32	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?				
DATASETS					
33	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?				
34	Has the applicant submitted datasets in the format agreed to previously by the Division?				
35	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				

	Content Parameter	Yes	No	N/A	Comment
36.	Are all datasets to support the critical safety analyses available and complete?				
37.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				
CASE REPORT FORMS					
38.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?				
39.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?				
FINANCIAL DISCLOSURE					
40.	Has the applicant submitted the required Financial Disclosure information?				
GOOD CLINICAL PRACTICE					
41.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?				

NONCLINICAL FILING CHECKLIST

IMPORTANT: This checklist is a sample of a tool used to assist reviewers during the filing review of an application. All decisions regarding whether an application can be filed are based on a comprehensive review of all relevant information in accordance with applicable legal and scientific standards.

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			
2	Is the pharmacology/toxicology section indexed, paginated, and legible in a manner allowing substantive review to begin?			
3	Has a summary of the nonclinical pharmacology and toxicology section of the NDA or BLA been submitted appropriately (in accordance with 505(b)(1), 505(b)(2), 351(a), or 351(k), whichever is applicable)?			
4	Are full reports of all nonclinical studies or risk assessments to establish the drug product's safety (in accordance with 505(b)(1), 505(b)(2), including referenced literature, 351(a), or 351(k), as appropriate) completed and submitted? (For example, are pharmacology, safety pharmacology, ADME [absorption, distribution, metabolism, excretion], general toxicology, genetic toxicology, carcinogenicity, developmental and reproductive toxicology studies and/or risk assessments, etc. completed and submitted, as appropriate?)			
5	Has appropriate information been submitted related to the safety qualification of the to-be-marketed formulation? If novel excipients are			

	proposed, or if the to-be-marketed formulation differs importantly from that used in nonclinical studies, adequate data and/or justification should be provided.			
6	Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route? (For clinical routes of administration other than the oral route, some nonclinical studies can be conducted by routes that differ from the clinical route as appropriate and/or recommended by FDA.)			
7	Has the applicant submitted a statement(s) that all pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			
8	Has the applicant submitted all information requested by the FDA during pre-submission discussions?			
9	Have proposed labeling sections relative to pharmacology/toxicology (including animal-to-human exposure multiples, e.g., mg/m^2 or AUC ratios) and in accordance with 21 CFR §201.57 been submitted?			
10	Have safety assessments of relevant impurities (e.g., manufacturing impurities, degradants, extractables/leachables, nitrosamines, as appropriate) been submitted? (Additional toxicity studies may not be needed.)			
11	If this NDA/BLA is to support a Rx to nonprescription switch, have all relevant studies and/or scientific justification been submitted?			

12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not own or have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they submitted a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			
13	Has the applicant submitted a statement identifying the Established Pharmacologic Class of the drug for product labeling, as appropriate. If a new pharmacologic class, has the applicant submitted rationale to address the proposed Established Pharmacological Class in accordance with 21 CFR 201.57(a)(6).			
14	Have required SEND datasets been submitted for the appropriate nonclinical studies? (SEND requirements are based on study initiation date and study type.)			

BIOSTATISTICS FILING CHECKLIST

IMPORTANT: This checklist is a sample of a tool used to assist reviewers during the filing review of an application. All decisions regarding whether an application can be filed are based on a comprehensive review of all relevant information in accordance with applicable legal and scientific standards.

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

[*Note to reviewer: In this section provide a summary of the clinical trials that will be reviewed in your statistical assessment of the NDA/BLA. See Table 1 below for an example summary of the trials. Additional information to consider including in this section would be whether any of the submitted trials were reviewed under an SPA, a discussion regarding the ability of the submitted trials to support the sponsor's proposed labeling claims and a discussion of trials that will not be reviewed and why.]*

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
T0001	MC, R, DB, PG, PC trial (12 wks)	Drug A/ N_A Placebo/ N_P	Primary: Key Secondary:	
T0002	MC, R, DB, PG, AC (24 wks)	Drug A/ N_A Control/ N_C	Primary: Key Secondary:	

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled

2. Assessment of Protocols and Study Reports

[*Note to reviewer: The following section should be addressed based upon review of the protocol(s) and the study report submitted for each trial referenced in Table 1 above. The reviewer is encouraged to provide details in the "Response/Comments" column of Table 2.*]

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	
Interim analyses (if present) were pre-specified in the protocol with appropriate associated analyses. DSMB meeting minutes and data are available.	
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	

3. Electronic Data Assessment

[*Note to Reviewer: The following section is meant to document the details as they pertain to the electronic data submitted in the application.*]

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	
Were analysis datasets provided?	
Dataset structure (e.g., SDTM or ADaM)	
Are the define files sufficiently detailed?	
List the dataset(s) that contains the primary endpoint(s)	
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

[*Note to Reviewer: This information is needed or essential to be able to review the application.*]

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc..				
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.).				
Safety and efficacy were investigated for sex, racial, ethnic, and geriatric subgroups.				
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).				
Application appears to be free from any other deficiency that render the application				

Content Parameter	Yes	No	NA	Comments
unreviewable, administratively incomplete, or inconsistent with regulatory requirements.				

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE? Yes / No

5. Comments to be Conveyed to the Applicant

[*Note to Reviewer: In this section provide all comments that should be conveyed to the sponsor. Section 5.1 "Refuse-to-File Information Requests" should be based upon deficiencies identified in Section 4 of the Filing Review. Section 5.2 "Information Requests/Review Issues" should be used to request any additional information that would facilitate the review or to note any review issues identified by the time of filing that are meant to be conveyed to the sponsor. All comments in this section should be written in such a way that they can be copied by the project management staff.*]

5.1. Refuse-to-File Issues

5.2. Information Requests/Review Issues

6. Advisory Committee

	Response/Comments
If the Advisory Committee Decision Aid (ACDA) is required for this application (it is required for a new molecular entity or original BLA), do you have any comments relevant to the completion of this document?	
Has the review division determined that an Advisory Committee (AC) meeting is needed?	☐ Yes ☐ No ☐ To be Determined
If an AC meeting may be held for this application, are there any areas of expertise that may be important for AC statistician(s) to have?	

CLINICAL PHARMACOLOGY FILING CHECKLIST

IMPORTANT: This checklist is a sample of a tool used to assist reviewers during the filing review of an application. All decisions regarding whether an application can be filed are based on a comprehensive review of all relevant information in accordance with applicable legal and scientific standards

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☐ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☐ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☐ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☐ Yes ☐ No	Clinical Pharmacology Summary	☐ Yes ☐ No
Bioanalytical and Analytical Methods	☐ Yes ☐ No	Labeling	☐ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☐ Relative Bioavailability		
☐ Bioequivalence		

☐ Food Effect					
☐ Other					
Human Pharmacokinetics					
Healthy Subjects	☐ Single Dose				
	☐ Multiple Dose				
Patients	☐ Single Dose				
	☐ Multiple Dose				
☐ Mass Balance Study					
☐ Other (e.g. dose proportionality)					
Intrinsic Factors					
☐ Race					
☐ Sex					
☐ Geriatrics					
☐ Pediatrics					
☐ Hepatic Impairment					
☐ Renal Impairment					
☐ Genetics					
Extrinsic Factors					
☐ Effects on Primary Drug					
☐ Effects of Primary Drug					
Pharmacodynamics					
☐ Healthy Subjects					
☐ Patients					
Pharmacokinetics/Pharmacodynamics					
☐ Healthy Subjects					
☐ Patients					
☐ QT					
Pharmacometrics					
☐ Population Pharmacokinetics					
☐ Exposure-Efficacy					
☐ Exposure-Safety					
☐ Physiologically-Based Pharmacokinetics					
Total Number of Studies			**In Vitro**		**In Vivo**
Total Number of Studies to be Reviewed					

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☐N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☐Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☐N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☐Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☐Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☐Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☐Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☐N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☐Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☐N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☐Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☐N/A	

PRODUCT QUALITY FILING CHECKLIST – NDA

IMPORTANT: This checklist is a sample of a tool used to assist reviewers during the filing review of an application. All decisions regarding whether an application can be filed are based on a comprehensive review of all relevant information in accordance with applicable legal and scientific standards.

For Yes/No boxes: Place "X" in appropriate box.

A. Conclusion				
	Parameter	**Yes**	**No**	**Comment**
1	Does OPQ Recommend the Application to be filed?			
2	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Describe filing issues here or on additional sheets
3	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?			Describe potential review issues here or on additional sheets

B. Overview of Critical Product Quality Review Considerations
Briefly describe the indication, the product and the process, and elements that are critical to the evaluation of product quality and the benefit-risk assessment (e.g., NME, breakthrough designation, specialty population, emerging technology elements, narrow therapeutic, combination product, biosimilar, complex API/dosage form/delivery system, advanced manufacturing or control strategy elements, sterility assurance, EA team, established conditions proposed).

C. Submission Content					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report (NME, API with estrogenic, androgenic, or thyroid activity; API derived from plants and animals) or appropriate categorical exclusion (21 CFR 25.15(d) and 25.31) been provided?				
2.	For DMFs, are DMF #s identified and authorization letter(s) from the US agent provided in the application and referenced DMF?				
3.	Is the Quality Overall Summary (QOS) organized adequately? Is there sufficient information in the QOS to conduct a review?				
FACILITY INFORMATION					
4.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing/ laboratory sites identified on Form FDA 356h or associated continuation sheet? For a naturally-derived DS only, are the facilities responsible for critical intermediate or crude DS manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: • Name of facility • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number, and e-mail for on-site contact person. • Is the manufacturing responsibility and function identified for each facility				

C. Submission Content					
5.	Does the Form FDA 356h indicate that all facilities are ready for inspection at the time of submission?				
DRUG SUBSTANCE INFORMATION					

6.	Is the Drug Substance section [3.2.S] organized adequately? Is there sufficient information in this section to conduct a review?
	• Manufacturer information including the establishment information submitted in Form FDA 356h or associated continuation sheet, and any other establishments contributing data to the application
	  o Name and full address(es) of the facility(ies)
	  o Contact name, phone number, email address
	  o Specify function or responsibility
	  o Type II DMF number(s) for API(s)
	  o Additional sources of API and information, if applicable
	• Characterization of drug substance
	• Control of drug substance
	  o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred)
	  o Includes specification, including analytical methods, and data demonstrating specification is met. Includes analytical method validation for non-compendial methods, verification for USP methods
	• Reference standards or materials
	• Container closure system				

C. Submission Content					
	• Stability o Includes data establishing stability of the product through the retest date or expiration date and the stability protocol describing the test methods and time intervals for product assessment				
DRUG PRODUCT INFORMATION					

7.	Is the Drug Product section [3.2.P] organized adequately? Is there sufficient information in this section to conduct a review?
	• Description and Composition of the Drug Product
	• Pharmaceutical Development
	  o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots
	  o Includes complete description of product lots and their uses during development
	• Manufacturer information, including the establishment information submitted in the Form 356h or associated continuation sheet for the finished dosage manufacturer and all outside contract testing laboratories, and any other establishments contributing data to the application
	  o Name and full address(es) of the facility(ies)
	  o Contact name, phone number, email address
	  o Specify function or responsibility
	  o Description of manufacturing process and process controls				

C. Submission Content					
	○ Description of the manufacturing process Information on control of critical steps and intermediates ○ If sterile, are relevant sterilization and depyrogenation validation studies submitted or a Letter of Authorization provided if a DMF is referenced • Control of Excipients • Control of Drug Product ○ Includes specification, including analytical methods, and data demonstrating specification is met ○ Includes data to justify the equipment and process controls of the proposed commercial batches ○ Includes data to demonstrate comparability of product to be marketed that was used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ○ Includes analytical method validation for non-compendial methods, verification for USP methods • Container Closure System • Stability ○ Includes data establishing stability of the product and a proposed shelf life based on available data, and the				

C. Submission Content					
	stability protocol describing the test methods and time intervals for product assessment				
BIOPHARMACEUTICS					
8.	Is there justification provided for in vitro dissolution/release specification of the proposed drug product?				
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of different formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies*) Is there justification provided for scientific bridging for 505 b (2) product to Listed Product per 21 CFR Part 320?				
10	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under 21 CFR part 320 to support the requested waiver? Note the CFR section cited.				
11	For a modified release dosage form, does the application include information/data on the in vitro alcohol dose-dumping potential?				
12	For an extended-release dosage form, is there enough information to assess the extended release designation claim as per 21 CFR 320.25(f)?				
13	Is there a claim or request for BCS designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?				
REGIONAL INFORMATION AND APPENDICES					
14	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?				

C. Submission Content					
15	Are Executed Batch Records for drug substance (if applicable) and drug product available?				

PRODUCT QUALITY FILING CHECKLIST – BLA

IMPORTANT: This checklist is a sample of a tool used to assist reviewers during the filing review of an application. All decisions regarding whether an application can be filed are based on a comprehensive review of all relevant information in accordance with applicable legal and scientific standards.

For Yes/No boxes: Place "X" in appropriate box.

D. Conclusion				
	Parameter	**Yes**	**No**	**Comment**
1.	Does OPQ Recommend the application be filed?			
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Describe filing issues here or on additional sheets
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?			Describe potential review issues here or on additional sheets

Note: For Table B, where you see a superscript with "1": contact the Office of Pharmaceutical Quality Research and/or Emerging Technology Team for assessment team considerations.

For Yes/No boxes: Place "X" in appropriate box.

B. Noteworthy Elements of the Application				
#	Product Type:	Yes	No	Comment
1.	Botanical			
2.	Natural-derived product			
3.	Narrow Therapeutic Index (NTI) Drug			
4.	Radiolabeled Product			
5.	Biosimilar product			
6.	Combination product			
7	Other: fill in			
#	Regulatory considerations:	Yes	No	Comment
8.	USAN Name			
9.	End of Phase II/Pre-BLA Agreement			
10.	**SPOTS (special products on-line tracking system)**			

11.	**Citizen Petition and/or prior correspondence linked to the application**				
12.	Comparability protocol(s) or PACMP				
13	Established conditions proposed				
14.	Other:				
#	Quality considerations:		Yes	No	Comment
15.	Drug Substance Overage				
16.	Design Space	Formulation			
17.		Process			
18.		Analytical Methods			
19.		Other			
20.	Real Time Release Testing				
21.	**Parametric Release in lieu of Sterility Testing**				
22.	**Alternative Microbiological Test Methods**				
23.	Process Analytical Technology[1]				
24.	Non-compendial Analytical Procedures and Specifications	Drug Product			
25.		Excipients			
26.		Microbial			
27.	Unique analytical methodology[1]				
28.	Excipients of Human or Animal Origin				
29.	Novel Excipients				
30.	Nanomaterials[1]				
31.	Hold Times Exceed 30 days				
32.	Genotoxic Impurities or Structural Alerts				
33.	Continuous Manufacturing[1]				
34.	Other unique manufacturing process[1]				
35.	New Delivery system or dosage form[1]				
36.	New product design[1]				
37.	Other: fill-in:				

For Yes/No/"N/A" boxes: Place "X" in appropriate box.

C. Submission Content					
GENERAL/ADMINISTRATIVE					
#	Parameter	Yes	No	N/A	Comment
1.	Has an environmental assessment report or appropriate categorical exclusion (21 CFR 25.15(d) and 25.31) been provided?				
2.	Is the Quality Overall Summary (QOS) organized adequately? Is there sufficient				

	information in the QOS to conduct a review?				

3.	In Module 3, is there sufficient information in the following sections to conduct an assessment?
	• Drug Substance
	• Drug Product
	• Appendices
	  o Facilities and equipment
	  o Adventitious Agents Safety Evaluation
	  o Novel Excipients
	• Regional Information
	  o Executed Batch Records
	  o Method Validation Package
	  o Product Life Cycle Management (PLCM) document, if applicable
	  o Comparability Protocols
	• Comparative Analytical Assessment (Biosimilars only)				

FACILITY INFORMATION					
4.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing/ laboratory sites identified on Form FDA 356h or associated continuation sheet? For a naturally-derived DS only, are the facilities responsible for critical intermediate or crude DS manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: • Name of facility • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA)				

	• Full name and title, telephone, fax number, and e-mail for on-site contact person. • Is the manufacturing responsibility and function identified for each facility • Is additional info such as BLA for further manufacture or DMF number provided, if applicable?				
5.	Does the Form FDA 356h indicate that all facilities are ready for inspection at the time of submission? • Is a manufacturing schedule provided? • Is the schedule feasible to conduct an inspection within the assessment cycle?				
DRUG SUBSTANCE INFORMATION					
6.	Is the Drug Substance section (3.2.S) organized adequately and supporting files and images legible? Is there sufficient information in the following sections to conduct an assessment? • General Information • Manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes description of any changes in the manufacturing process from material used in clinical to commercial production lots. o Includes complete description of product lots and their uses during development Characterization of drug substance Control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the				

	clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes specification, including analytical methods, and data demonstrating specification is met. Includes analytical method validation for non-compendial methods, verification for USP methods. o Includes data to demonstrate process consistency (i.e., data on process validation lots) Reference standards or materials Container closure system Stability o includes data establishing stability of the DS and a proposed shelf-life/retest period based on available data and a stability protocol describing the test methods and time intervals for sample assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product Section (3.2.P) organized adequately and supporting files and images legible? Is there sufficient information in the following sections to conduct an assessment? • Description and Composition of the Drug Product • Pharmaceutical Development o Includes descriptions of any changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development • Manufacture				

	○ If sterile, are relevant sterilization and depyrogenation validation studies submitted or a Letter of Authorization(s) provided if a DMF is referenced? ○ For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? Control of Excipients Control of Drug Product ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e., data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed that was used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution Reference Standards or Materials Container Closure System Stability ○ Includes data establishing stability of the product and a proposed shelf-life based on available data and the stability protocol describing the test methods and time intervals for product assessment				
REGIONAL INFORMATION AND APPENDICES					
8.	Are any study reports or published articles in a foreign language? If yes,				

	has the translated version been included in the submission for assessment?				
9.	Are Executed Batch Records for drug substance (if applicable) and drug product available?				
10.	Is the following information available in the Appendices for Biotech products [3.2.A]? • Facilities and Equipment o Manufacturing flow; adjacent areas o Other products in facility o Equipment dedication, preparation, sterilization, and storage o Procedures and design features to prevent contamination and cross-contamination Adventitious agents safety evaluation (viral and non-viral), e.g.: o Avoidance and control procedures o Cell-line qualification o Other materials of biological origin o Viral testing of unprocessed bulk o Viral clearance studies o Testing at appropriate stages of production Novel excipients				
11.	Is the following information available: • Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma				

REGULATORY PROJECT MANAGEMENT FILING REVIEW

IMPORTANT: This checklist is a sample of a tool used to assist reviewers during the filing review of an application. All decisions regarding whether an application can be filed are based on a comprehensive review of all relevant information in accordance with applicable legal and scientific standards.				
Format and Content (must be in eCTD format)				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
Index: Does the submission contain an accurate comprehensive index?	☐	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: • Legible • English (or translated into English) • Pagination • Navigable hyperlinks **If no**, explain.	☐	☐		
Forms and Certifications				
Electronic *forms with electronic signatures are required.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☐	☐		

Are all establishments and their registration numbers listed on the form/attached to the form?	☐	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the applicant or an authorized representative (see 21 CFR 54.2(g) and 54.4(a)(1)). If financial disclosure forms are signed by an authorized representative (e.g., a US agent) and not the applicant, request confirmation that the representative is authorized to sign on the applicant's behalf.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☐	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☐	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].***	☐	☐	☐	

Note: *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is a Field Copy Certification included? • Check eCTD section 1.3.2 for copy of letter notifying the District office that eCTD submission will be submitted to FDA, per the eCTD Technical Conformance Guide (the field offices have access to the EDR). ***If no, request a copy of the letter from the applicant. If applicant did not notify the District office prior to submission, request that applicant provide notification and submit a copy of the letter before the filing date.*** ***Note:*** *Field Copy Certification is not needed if there is no CMC technical section*	☐	☐	☐	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?	☐	☐	☐	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☐	☐		

If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue***	☐	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue.***	☐	☐	☐	
BPCA: Is this submission a complete response to a pediatric Written Request?	☐	☐		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted?	☐	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted?	☐	☐	☐	
Pharmacovigilance Plan (PVP) or Risk Management Plan (RMP)	**YES**	**NO**	**NA**	**Comment**
Is a PVP or RMP submitted?	☐	☐	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☐ Prescribing Information (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MG) ☐ Carton labeling ☐ Immediate container label(s) ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? *If no, request applicant submit SPL before the filing date.*	☐	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[25] *If no, request applicant submit labeling in PLR format before the filing date.*	☐	☐		

[25] To see an example of a PLR-formatted Labeling, see the "Sample Prescribing Information Template" under the Format Tools and Sample Templates heading on the Prescribing Information Resources webpage available at https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/prescribing-information-resources

Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?[26] *If no, request applicant submit labeling in PLLR format before the filing date.*	☐ ☐	☐ ☐	☐ ☐	
Nonprescription Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton labeling ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	**YES** ☐	**NO** ☐	**NA**☐	**Comment**
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	**YES** ☐	**NO** ☐	**NA**☐	**Comment**
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	**YES** ☐	**NO** ☐	**NA**☐	**Comment**
Environmental Assessment/ Categorical Exclusion	**YES** ☐	**NO** ☐	**NA**☐	**Comment**

[26] PLLR format labeling is required to have a Pregnancy subsection (subsection 8.1) and a Lactation subsection (subsection 8.2) and may have a Females and Males of Reproductive subsection (subsection 8.3). For more information, see https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-resources.