SOPP 8404: Refusal to File Procedures

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I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide for Center for Biologics Evaluation and Research (CBER) staff to follow for Refuse to File (RTF) determinations for a Biologics License Application (BLA), an Efficacy Supplement or a Prior Approval Manufacturing Supplement (21 CFR 601.2), or a New Drug Application (NDA) or supplemental NDA (21 CFR 314.101(d)(1)-(9)).

II. Scope

A. This SOPP applies to BLAs and associated efficacy or manufacturing supplements, as well as NDAs and associated supplemental NDAs for which an RTF decision is made.

B. This SOPP does not apply to BLAs subject to the Medical Device User Fee Act (MDUFA) or Abbreviated New Drug Applications subject to the Generic Drug User Fee Act (GDUFA).

III. Background

A. RTF is an important regulatory tool to help CBER avoid unnecessary review of incomplete applications and supplements. Incomplete submissions can lead to multiple-cycle reviews and inefficient use of CBER resources. CBER believes an RTF action can allow an applicant to address critical insufficiencies that do not permit a substantive review and to submit a complete new BLA that may permit a substantive review.

B. Applications and supplements are expected to be complete when received by the Agency. Incomplete applications and some supplements will be subject to an RTF decision.

C. Discipline-specific filing checklists or memos, if there is not a checklist, are used to ensure a timely and thorough filing review of applications, to provide consistency in applying our RTF authority, and to provide documentation of deficiencies for the RTF letter.

IV. Definitions

Not Applicable

V. Policy

A. RTF decisions are made on submissions that do not, on their face, contain information required under section 351 of the Public Health Service Act; the Federal Food, Drug, and Cosmetic Act (FD&C Act); or in the FDA regulations (e.g., § 601.2 for BLA and §314.50 for NDA). RTF decisions may be made based on findings such as:

1. Administrative incompleteness, e.g., clear omission of information or sections of required information.

2. Scientific incompleteness, such as omission of critical data, information or analyses needed to evaluate safety, purity and potency or provide adequate directions for use, including clinical information, quality, manufacturing, and facility information, pharmacology/toxicology information and/or critical statistical analyses or the analysis of a study as planned in the protocol (as opposed to a different, post-hoc analysis).

3. Inadequate content, presentation, or organization of information such that substantive and meaningful review is precluded, such as illegibility, failure to translate portions of the application into English, data tabulations (line listings) or graphical displays that are uninterpretable, failure to reference the location of individual data and records in summary reports; absence of protocols for clinical trials.

B. For products submitted under the PDUFA Program, a pre-BLA/NDA meeting occurs whereby the FDA and the applicant agree on the content of a complete application for the proposed indication(s) and identify minor components that may be submitted no later than 30 calendar days after receipt of the original application. Applications are expected to be complete when received by the Agency. Failure to submit agreed-upon minor components within 30 days will be subject to an RTF decision.

C. CBER's initial decision on whether to file an application or supplement will be based upon a threshold determination as to whether the information submitted to support licensure or approval is sufficiently complete to permit a substantive and meaningful review. CBER will attempt to rectify easily correctable deficiencies (refer to Appendix A for examples).

D. When an RTF is recommended by the review committee and before a final decision, internal discussions with senior Center leadership will be held to include the Office Director from the relevant review office with signatory authority for the letter, CBER's Associate Director for Policy, the Center Director and Deputy Center Director. Refer to *Job Aid (JA) 910.22: Procedures for Upper Center Management Leadership Briefing Before Issuing a Refuse-to-File Letter*.

E. An RTF is not a final determination concerning potential approvability or the scientific/medical merits of the application; instead, it is an early signal to the applicant that the application has omissions or inadequacies so severe as to render the application incomplete on its face or to introduce significant impediments to a prompt and meaningful review. It is an opportunity for the applicant to develop a complete, new submission.

F. RTF deficiencies are distinct from complete response (CR) deficiencies. CR deficiencies apply when a complete review of a filed application indicates that there are deficiencies that preclude the approval of the application based on the information provided at that time, e.g., balancing risks and benefits, magnitude of clinical effect, acceptability of a plausible surrogate marker, or nuances of study design.

VI. Responsibilities

A. Branch/Lab Chief, Division Director – Evaluates the reviewer's recommendations; concurs/does not concur on recommendation. Writes separate memo for a non-concurrence.

B. Chair/Regulatory Project Manager (RPM) – Drafts and finalizes Filing Meeting Summary and Filing or RTF letter; manages RTF process; ensures issuance of the Filing/RTF letter to the applicant.

C. Office Director – The Signatory Authority who signs RTF letters. Writes separate memo for a non-concurrence.

D. Review Committee Member – Reviews submission, recommends whether or not the submission can be filed, documents recommendation in the filing checklist or memo, discusses the filing recommendation with management, reviews draft meeting summary and draft Filing or RTF letter.

VII. Procedures

A. Original BLAs, NDAs and Efficacy Supplements

1. Before the Filing Meeting

a. Review the submission as described in *JA 910.06: Completing a Filing Review.* **[Review Committee Members]**

b. Ensure that the RTF briefing meeting has been scheduled as described in *JA 910.22: Procedures for Upper Center Management Leadership Briefing Before Issuing a Refuse-to-File (RTF) Letter*. **[RPM]**

c. Notify the Chair, RPM, and supervisors (Branch/Lab Chief, Division Director) of the potential for an RTF recommendation, if applicable. **[Review Committee Members]**

d. Draft and distribute the Filing Meeting Agenda in preparation for the Filing meeting. **[RPM]**

Note: Ensure CBER leadership and upper office management (division, office directors as appropriate to the issue) are invited if there are significant review or potential RTF issues. (Refer to *R 910.02: Attendee Table for BLA/NDA Meetings* for complete list of recommended attendees).

e. Ensure that upper office management (i.e., Division Directors, Office Director) is notified immediately upon discovering that an RTF recommendation might be made. **[Chair/RPM]**

f. Complete the filing checklists or memo, summarize all potential review deficiencies and RTF items in letter ready format in the appropriate section of the checklist or memo. **[Review Committee Members]**

g. Email the checklists or memo, with the appropriate management copied, to the Chair and RPM before the filing meeting. **[Review Committee Members]**

h. Discuss and decide whether the submission should or should not be filed at the filing meeting. **[Review Committee Members, Branch/Lab Chief, Division Director, Office Director**

Note: if submission will be filed, proceed with review as outlined in *SOPP 8401: Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA).*

2. After Filing Meeting - Filing Checklists/Memos

a. Update the filing checklist or memo, if needed, and include a rationale if recommending an RTF decision in the appropriate section of the filing checklist or memo. The RTF recommendation must include a list of deficiencies. **[Review Committee Members]**

b. Sign the filing checklist or memo; send for supervisory review and concurrence. **[Review Committee Members]**

c. Perform a secondary review of the signed checklist or memo to determine concurrence on the filing decision, rationale, and any letter ready comments. **[Branch/Lab Chief, Division Director]** Note: any non-concurrence must be accompanied by a written explanation/memo and included in the administrative file per standard procedures.

d. Upload the filing checklist or memo after secondary review is completed into the appropriate regulatory system through CBER Connect. **[Review Committee Members]**

3. After Filing Meeting - Meeting Summary/RTF Letter

a. Draft the Filing Meeting Summary and document the recommendation which should include the rationale for not filing the submission and a list of deficiencies. **[RPM/Chair]**

b. If an RTF is recommended, ensure that the Office Director from the relevant review office with signatory authority for the letter, CBER's Associate Director for Policy, the Center Director and Deputy Center Director are briefed on the recommendation. Refer to *JA 910.22: Procedures for Upper Center Management Leadership Briefing Before Issuing a Refuse-to-File (RTF) Letter* for procedures and *R 910.02: Attendee Table for BLA/NDA Meetings* for complete list of recommended attendees. **[RPM]**

c. Draft the Refuse to File letter using the current CBER letter template (refer to CBER's Review Letter Templates in ORO's SharePoint Online

(SPO) library for the most recent approved template). Include the following: **[RPM]**

i. The deficiencies that form the basis for the RTF decision.

ii. The option to protest the Agency's decision and request that CBER file and review the application over protest (FOP), as well as a web site link to *SOPP 8404.1: Procedures for Filing an Application When the Applicant Protests a Refusal to File Action (File Over Protest)*.

d. Send draft Filing Meeting Summary and RTF Letter to Review Committee Members, Branch/Lab Chief, Division Directors and Office Directors for concurrence. **[RPM]**

e. Review Filing Meeting Summary and RTF Letter for accuracy and completeness and provide feedback to RPM. **[Review Committee Members, Branch/Lab Chief, Division Directors, Office Directors]**

f. Obtain concurrence on the Filing Meeting Summary and RTF Letter. The signature authority for RTF Letter is the Office Director or designee. **[RPM]**

g. Enter Filing Meeting Summary and RTF Letter into the appropriate regulatory system through CBER Connect. **[RPM]**

h. Ensure that the RTF letter is sent to the applicant within 60 days of the CBER receipt date. **[RPM]**

i. Follow *DCC Procedure Guide #8 Procedure for Filing Final Action Packages Containing FDA Correspondence For Marketing Applications* or *DCC Procedure Guide #23 Procedure for Filing Final Action Packages Containing Electronic FDA Communication for Marketing Applications* as applicable to complete the final action package processing. **[RPM, Review Committee Members]**

B. Manufacturing Supplements

1. Review submission for completeness and adequacy of contents and potential refuse to file issues before day 30. **[Review Committee Members]**

2. Notify the Chair, RPM, supervisors (Branch/Lab Chief, Division Director, Office Director) of the potential of an RTF recommendation. **[Review Committee Members]**

3. Determine whether the submission should or should not be filed. **[Review Committee Members, Branch/Lab Chief, Division Director, Office Director]**

4. If an RTF decision is made, document the RTF issue(s) in a memorandum which includes the rationale and the list of deficiencies. **[Review Committee Members]**

   Note: if the decision is to file the supplement, refer to *SOPP 8401.2: Administrative Processing of BLAs and NDA Supplements* for filing procedures.

5. Notify CBER leadership when an RTF decision has been made. **[RPM]**

6. Sign and send the memorandum for supervisory review and concurrence. Upload the memorandum into the appropriate regulatory system through CBER Connect. **[Review Committee Members]**

   Note: any supervisory non-concurrence must be accompanied by a written explanation/memo and included in the administrative file per standard procedures.

7. Draft the RTF letter using the current CBER letter template (refer to CBER's Review Letter Templates in ORO's SPO library for the most recent approved template). Include the following: **[RPM]**

   a. The deficiencies that form the basis for the RTF decision.

   b. The option to protest the Agency's decision and request that CBER file and review the application over protest (FOP), as well as a web site link to *SOPP 8404.1: Procedures for Filing an Application When the Applicant Protests a Refusal to File Action (File Over Protest)*.

8. Send RTF Letter to Review Committee Members, Branch/Lab Chief, Division Directors, and Office Directors for concurrence. **[RPM]**

9. Review RTF Letter for accuracy and completeness and provide feedback to RPM. **[Review Committee Members, Branch/Lab Chief, Division Directors, Office Directors]**

10. Obtain concurrence on the RTF Letter. The signature authority for RTF Letter is the Office Director or designee. **[RPM]**

11. Enter and upload the RTF Letter into the appropriate regulatory system through CBER Connect. **[RPM]**

12. Ensure that the RTF letter is sent to the applicant within 60 days of the CBER receipt date. **[RPM]**

13. Follow *DCC Procedure Guide #8 Procedure for Filing Final Action Packages Containing FDA Correspondence For Marketing Applications* or *DCC Procedure Guide #23 Procedure for Filing Final Action Packages Containing Electronic FDA Communication for Marketing Applications* as applicable to complete the final action package processing. **[RPM, Review Committee Members]**

VIII. Appendix

A. Examples of Easily Correctable Deficiencies

B. Discipline Filing Checklists for BLA, NDA, and Efficacy Supplements

IX. References

A. References below are CBER Internal:

1. JA 910.06: Completing a Filing Review

2. JA 910.22: Procedures for Upper Center Management Leadership Briefing Before Issuing a Refuse-to-File (RTF) Letter

3. R 910.02: Attendee Table for BLA/NDA Meetings

4. DCC Procedure Guide #8: Procedure for Filing Final Action Packages Containing FDA Correspondence For Marketing Applications

5. DCC Procedure Guide #23: Procedure for Filing Final Action Packages Containing Electronic FDA Communication for Marketing Applications

B. References below can be found on the Internet:

1. Guidance for Industry: Providing Regulatory Submissions in Electronic Format: Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

2. SOPP 8401: Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA)

3. SOPP 8401.2: Administrative Processing of BLAs and NDAs Supplements

4. SOPP 8404.1: Procedures for Filing an Application When the Applicant Protests a Refusal to File Action (File over Protest)

X. History

Written/Revised	Approved	Approval Date	Version Number	Comment
Raza/Valencia/Rivers	Sonday Kelly, MS, RAC, PMP Director, DROP/ORO	December 15, 2025	12	Updated to include Discipline Filing Checklists for BLA, NDA, and Efficacy Supplements in Appendix B.
Iliana Valencia	Sonday Kelly, MS, RAC, PMP Director, DROP/ORO	August 29, 2024	11	Updated RTF examples under policy; incorporated policy from previous Appendix A into Policy section and updated appendix A to list examples of easily correctible deficiencies; minor clarifications in procedures; minor formatting editing.
Martha Monser	Sonday Kelly, MS, RAC, PMP Director, DROP/ORO	September 22, 2023	10	Updated to include an Upper Center Management briefing if a RTF is recommended.
Martha Monser	N/A	December 11, 2022	9	Technical Update: Replace “database” with “system”
Martha Monser	N/A (Reviewed by Job Aid Coordinator)	January 6, 2020	8	Technical Update: new format/font and corrections to reference titles and URLs
Martha Monser	Christopher Joneckis, PhD	March 11, 2018	7	Update for consistency with electronic filing requirements and to include manufacturing supplements
Martha Monser	Christopher Joneckis, PhD	September 1, 2017	6	Technical Update for PDUFA VI and removal of previous Appendix A (FR 38771 notice)
Linda Dixon	Christopher Joneckis, PhD	January 17, 2017	5	Updated for consistency with JA 910.06
Sandra Menzies	Christopher Joneckis, PhD	July 2, 2015	4	Update to use Filing Checklists to support RTF

Written/Revised	Approved	Approval Date	Version Number	Comment
RMCC/Lydia Falk	Robert A. Yetter, PhD	August 22, 2007	3	Corrects link to CBER's RTF philosophy as per Federal Register notice (#38771)
Leonard Wilson	Robert A. Yetter, PhD	October 2, 2002	2	Clarifies roles and responsibilities, adds reference to FOP procedures.
CBER Application Policy Task Force	Michael Beatrice	November 1, 1993	1	Reissued as SOPP 8404 in August 1997. No change to Guide Content (OD-R-2-93)

SOPP 8404 Appendix A*:* Examples of Easily Correctable Deficiencies

This appendix provides examples of potentially easily correctible deficiencies. 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.

1. Electronic navigational problems.
2. Electronic non-compatibility or readability with the FDA's system.
3. Incomplete or missing Form FDA 356h (Application to Market a New or Abbreviated New Drug or Biologic for Human Use).
4. Incomplete electronic dataset(s) or missing components and technical issues or missing key components on datasets.
5. Missing financial disclosure statement on From FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and/or From FDA 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators).
6. Small amounts of missing data (e.g., collected but not submitted).
7. Failure to submit the content of labeling in electronic structure product labeling (SPL) format as described in 21 CFR 314.50(1)(1)(i) for NDAs and supplements and 21 CRF 601.14(b) for BLAs and supplements.
8. For NDAs, missing right of reference to information required for an application.
9. For NDAs, an incorrectly worded Debarment Certification statement.

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Appendix B: Discipline Filing Checklist for BLA, NDA, and Efficacy Supplements

Regulatory Project Manager 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.

Overall Format/Content

	Overall Format/Content	YES	NO	NA	Comment
1.	**Does electronic submission follow the eCTD guidance?** **If not,** explain (e.g., waiver granted).				
2.	**Does the submission contain an accurate comprehensive index?** (e.g., table of contents)				
3.	**Is the submission complete including a-f?** As required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) ***If any of the following are "no"**, explain why (i.e., datasets are not in correct format):				
	a. Legible*				
	b. English* (or translated into English)				
	c. Pagination*				
	d. Navigable hyperlinks* (electronic submissions only)				
	e. Datasets present in software compatible format*				
	f. All sections are present*				

	Overall Format/Content	YES	NO	NA	Comment
4.	**Companion application received?** Shared or divided manufacturing arrangement (***BLA only***) or, cross-reference to Master File received for proprietary information not included with submission. If yes, insert companion application BLA # or cross-referenced Master File #				

Applications in The Program (PDUFA)

	Applications in The Program (PDUFA)	YES	NO	NA	Comment
5.	**Were there agreements made at the applicant's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?**				
	a. **If so, were the late submission components all submitted within 30 days?** List any late submission components which arrived after 30 days in the comments box.				

Forms and Certifications

Application Form

	Application Form	YES	NO	NA	Comment
6.	**Is Form FDA 356h included with authorized signature per 21 CFR 601.2(a) (BLAs) or per 21 CFR 314.50(a) (NDAs)?**				
	a. If foreign applicant, has a U.S. agent signed the form [see 21 CFR 314.50(a)(5) (NDAs)]?				
	b. Is a comprehensive and readily located list of all clinical sites listed on the form or attached to the form?				

	Application Form	YES	NO	NA	Comment
	c. Are all establishments and manufacturing facilities, along with their registration numbers, listed on the form or attached to the form?				

Financial Disclosure

	Financial Disclosure	YES	NO	NA	Comment
7.	**Are financial disclosure forms, Form 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, not an Agent [see 21 CFR 54.2(g)].***				

Clinical Trials Database and Study Data

	Clinical Trials Database & Study Data	YES	NO	NA	Comment
8.	**Is Form FDA 3674 included with authorized signature?**				
9.	**Are National Clinical Trial (NCT) Numbers included on 3674?**				
10.	**Study Data Tabulation Model (SDTM), Analysis Data Model (ADaM) data in eCTD Module 5 is present?**				
11.	**Is study data acceptable based on the validation reports?**				

Debarment Certification

	Debarment Certification	YES	NO	NA	Comment
12.	**Is a correctly worded Debarment Certification included with authorized signature?** *Certification is not required for supplements if the debarment certification was submitted in the original application.*				

Exclusivity

	Exclusivity	YES	NO	NA	Comment
13.	**Does another product (same drug (BLAs) or same active moiety (NDAs)) have orphan exclusivity for the same indication?**				
14.	**If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]?**				
15.	**Has the applicant requested reference product designation and 12-year exclusivity?**				
16.	**Has the applicant requested pediatric exclusivity under BPCA?**				

Priority Review Voucher Requests

	Priority Review Voucher Requests	YES	NO	NA	Comment
17.	**Has the applicant requested a Priority Review Voucher?** **Indicate voucher type below:**				
	a. Rare Pediatric Disease request?				
	b. Material Threat Medical Counter Measures (MCM) request?				
	c. Tropical disease request?				

Pediatrics

	Pediatrics	YES	NO	NA	Comment
18.	**Does the application trigger PREA? Pediatric Research Equity Act (PREA)**				
	a. If yes, has the applicant included or referenced the agreed upon pediatric study plan (PSP)?				

	Pediatrics	YES	NO	NA	Comment
	b. If yes, has the applicant submitted the pediatric assessment, or provided documentation requesting either a waiver and/or deferral in accordance with their agreed PSP?				
19.	**Does the submission include a pediatric assessment in response to a deferred Pediatric study?**				

Proper Name and Suffix

	Proper Name and Suffix	YES	NO	NA	Comment
20.	**Is a proper name submitted?**				
21.	**Are proposed suffix(es) included in submission?**				

Proprietary Name

	Proprietary Name	YES	NO	NA	Comment
22.	**Is a proposed proprietary name submitted?**				

REMS

	REMS	YES	NO	NA	Comment
23.	**Is a REMS submitted?**				

Prescription Labeling-1

	Prescription Labeling	Check all types of labeling submitted.
24.	**a. United States Prescribing Information (USPI)**	
	b. Patient Package Insert (PPI)	
	c. Patient Oriented Labeling (POL)	
	d. Instructions for Use (IFU)	
	e. Medication Guide (MedGuide)	
	f. Package labels	
	g. Immediate container labels	
	h. Diluent	
	i. Other (specify):	

Prescription Labeling-2

	Prescription Labeling	YES	NO	NA	Comment
25.	**Is Electronic Content of Labeling (COL) submitted in SPL and Word format?**				
26.	**Is the PI submitted in Physicians Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) format?**				
27.	**All labeling (e.g., USPI, PPI, MedGuide, POL/IFU, carton and immediate container labels)**				

Clinical Review 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.

Format/Organization/Legibility

	Format/Organization/Legibility	YES	NO	NA	Comment
1	Is the clinical section organized in a manner to allow substantive review to begin?				
2	Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?				
3	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?				
4	Is it possible to navigate the application to allow a substantive review to begin, *e.g.*, are the bookmarks and hyperlinks adequate?				
5	Are all documents submitted in English or are English translations provided when necessary?				
6	Is the clinical section legible so that substantive review can begin, i.e., check for scanned pages or font size and type that are difficult or impossible to read?				

Labeling

	Labeling	YES	NO	NA	Comment
7	Has the applicant submitted draft labeling for the carton, container, and package insert (PI) in electronic format consistent with current regulation, divisional, and Center policies (including carton, container, and package inserted in PLR and PLLR formats: Word, and XML)?				

Summaries

	Summaries	YES	NO	NA	Comment
8	Has the applicant submitted the clinical overview?				
9	Has the applicant submitted the integrated summary of safety (ISS)?				
10	Has the applicant submitted the integrated summary of efficacy (ISE)?				
11	Has the applicant submitted a benefit-risk analysis for the product?				
12	Has the applicant submitted a post-marketing pharmacovigilance plan?				
13	If the pharmacovigilance plan proposes any new REMS, has the applicant submitted the supporting REMS materials in the file?				
14	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				

Dose

	Dose	YES	NO	NA	Comment
15	Has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product, *i.e.*, appropriately designed dose-ranging studies, if applicable?				
	Study Title:				
	Study Number:				
	Sample Size:				
	Arms:				
	Where in the submission can you find this information?				

Efficacy

	Efficacy	YES	NO	NA	Comment
16	Do there appear to be the requisite number of adequate and well-controlled studies in the application (at least 1 for an Efficacy Supplement)? **Pivotal Study #1:** National Clinical Trial#: Indication: **Pivotal Study #2:** National Clinical Trial#: 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.				
19	Has the applicant submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?				
20	If applicable, are studies that provide secondary support of efficacy/effectiveness included in a reviewable fashion in the BLA?				

Safety

	Safety	YES	NO	NA	Comment
21	Is the size of the safety database adequate and consistent with previous agreements between CBER and the applicant?				
22	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?				
23	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?				

	Safety	YES	NO	NA	Comment
24	If the biologic product is approved in other countries, has the applicant provided post-marketing safety data from those countries?				
25	Has the applicant submitted the coding dictionary used for mapping investigator verbatim terms to preferred terms?				
26	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?				
27	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?				

Other Studies

	Other Studies	YES	NO	NA	Comment
28	If applicable, has the applicant submitted all special studies/data, including pooled data analyses, requested by the Division during pre-submission discussions?				

Pediatrics

	Pediatrics	YES	NO	NA	Comment
29	**Pediatric Research Equity Act (PREA)** Does the application trigger PREA?			NA	
	a. If yes, has the applicant included or referenced the agreed upon pediatric study plan (PSP)?				
	b. If yes, has the applicant submitted the pediatric assessment, or provided documentation requesting either a waiver and/or deferral in accordance with their agreed PSP?				
30	Does the submission include a pediatric assessment in response to a deferred Pediatric study?				

Foreign Studies

	Foreign Studies	YES	NO	NA	Comment
31	If applicable, does the application include a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine?				

Datasets

	Datasets	YES	NO	NA	Comment
32	Has the applicant submitted datasets, line listings and/or tabular summaries in a format to allow reasonable review of the patient data?				
33	Has the applicant submitted datasets, line listings, and/or tabular summaries in the format agreed to previously by the Division?				
34	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				
35	Are all datasets, line listings and/or tabular summaries to support the critical safety analyses available and complete?				
36	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				

Case Report Forms

	Case Report Forms	YES	NO	NA	Comment
37	If required, has the applicant submitted Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?				
38	If applicable, has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?				
39	If applicable, has the applicant submitted an annotated Case Report Form that correlates with information in datasets?				

Good Clinical Practice

	Good Clinical Practice	YES	NO	NA	Comment
40	Is there a statement of Good Clinical Practice affirming that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?				

Nonclinical Filing Review 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
1.	Are the nonclinical sections organized in accord with current regulations and guidelines for eCTD content and format in a manner to allow substantive review to begin?				
2.	Are the nonclinical sections of the eCTD indexed and paginated in a manner allowing substantive review to begin?				
3.	Are the nonclinical sections of the eCTD legible so that substantive review can begin?				
4.	Are all required and requested IND/IDE, pre-BLA/NDA/PMA studies completed and submitted?				
5.	Is the product to be marketed different from the product tested in the nonclinical studies? If so, has the applicant submitted a rationale to justify the alternate approach?				
6.	Was the route of administration used in the animal studies the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternate route(s)?				
7.	Does each report for the pivotal toxicology studies include a statement that the study was performed in accordance with the GLP regulations (21 CFR 58)?				
a.	If not, has the applicant provided justification for why the study was not GLP-compliant?				
b.	Has the applicant specified any deviations from the prospective protocol, and their potential impact on study integrity and/or validity?				

	Content Parameter	Yes	No	N/A	Comment
8.	Are the proposed labeling sections relevant to the nonclinical data in the submission? If so, are they provided in the appropriate format in accordance with 21 CFR 201.57?				
9.	Has the applicant provided data regarding potential impurities (e.g., identification, amount, risk assessment)?				

Chemistry, Manufacturing, And Control Filing Review 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.

#	Item	Yes	No	N/A	Comments
	Format/Organization/Legibility				
1.	Includes a list of all establishment sites and their registration numbers.				
2.	Environmental assessment (EA) or request for categorical exclusion (CE) (21 CFR Part 25)				
3.	Reference Product Designation Request				
4.	Content, presentation, and organization of electronic components sufficient to permit substantive review? Examples include:				
	a. Legible				
	b. English (or translated into English)				
	c. Compatible file formats				
	d. Navigable hyper-links				
	e. Interpretable data tabulations (line listings) & graphical displays				
	f. Summary reports reference the location of individual data and records				
	g. Electronic submission components usable (e.g., conforms to published guidance)				
5.	Overall CTD Table of Contents				
6.	Introduction to the summary documents				
7.	Quality Overall Summary				
8.	Non-Clinical Overview				

#	Item	Yes	No	N/A	Comments
	Drug Substance and Drug Product				
9.	General Information				
	a. Nomenclature				
	b. Structure (e.g., sequence, glycosylation sites)				
	c. General Properties				
	d. Was a companion application received if a shared or divided manufacturing arrangement was used?				
	~~e.~~ Does the submission contain certification that all facilities are ready for inspection?				
	Manufacture				
10.	Manufacturer(s) (names, locations, registration numbers and responsibilities of all sites involved)				
11.	Description of manufacturing process and process controls				
	a. Batch numbering and pooling scheme				
	b. Cell culture and harvest				
	c. Purification				
	d. Filling, storage, and shipping				
12.	Control of materials				
	a. Control of raw materials NOT of biological origin				
	b. Animal derived reagents				
	c. Control of source and starting materials of biological origin (also described under product development)				
	d. Cell substrate source, history, and generation (e.g., vector and plasmids)				
	e. Cell banking system characterization and testing				

#	Item	Yes	No	N/A	Comments
	f. Seed virus source, history, and seed virus banking, characterization, and testing				
	g. Bacterial master and working seeds, source, history, passages, characterization, testing, and storage				
13.	Section to support animal husbandry and related information for transgenic products (includes a cross-reference to associated New Animal Drug Application (NADA))				
14.	Controls of Critical Steps and Intermediates				
	a. Justification of specifications and acceptance criteria				
	b. Hold times of intermediates				
15.	Process Validation and/or Evaluation (name, manufacturer) (prospective plan, results, analysis, and conclusions)				
16.	Manufacturing Process Development (Describe changes during non-clinical and clinical development; justification for changes)				
	a. Process comparability assessment, protocol and report				
	b. Risk assessment (if applicable)				
	Characterization of Drug Substance				
17.	Elucidation of Structure and other Characteristics				
18.	Impurities				

#	Item	Yes	No	N/A	Comments
	a. Removal of impurities by manufacturing process				
	Control of Drug Substance				
19.	Specification to ensure safety, identify, purity and potency of Drug Substance				
20.	Justification of Specification				
21.	Analytical procedures in sufficient details				
22.	Potency, purity, identity, safety, and microbial, endotoxin, and sterility testing				
23.	Validation of Analytical Procedures (validation reports)				
24.	Batch Analyses				
	Reference Standards or Materials				
25.	Container Closure System				
	a. Identity of materials of construction				
	b. Specifications				
	c. Description				
	d. Identification				
	e. Suitability				
	f. Leachables and extractables				
	Stability				
26.	Stability Summary and Conclusions				
27.	Post–approval Stability Protocol and Stability Commitment				
28.	Stability Data (e.g., shipping stability, shelf-life, dating period, etc.)				
	a. Pre-approval Stability Studies Detail (protocol, results, method validation)				
	b. Microbiological Attributes (e.g., bioburden and endotoxin, if appropriate)				
	Product: **Dosage Form:** **Manufacturer:**				

#	Item	Yes	No	N/A	Comments
29.	Description and Composition of the Drug Product				
	Pharmaceutical Development				
30.	Components of the Drug Product				
	a. Drug Substance				
	b. Excipients				
	c. Diluents, if appropriate				
31.	Drug product				
	a. Formulation Development Summary				
	b. Justification for Overages				
	c. Physiochemical and Biological Properties				
32.	Manufacturing Process Development for production through finishing, including formulation, filling, labeling, and packaging (including all steps performed at outside [e.g., contract] facilities)				
	a. Does the submission include complete descriptions of product lots and manufacturing process used for clinical studies?				
	b. Does the submission describe changes in the manufacturing process, from material used in clinical trial to commercial production lots?				
	c. If significant changes in manufacturing processes or facilities have occurred, are data demonstrating comparability of the product intended to be marketed against the product used in the clinical trials included in the submission?				

#	Item	Yes	No	N/A	Comments
33.	Container Closure System (Suitability of the container closure system)				
34.	Microbiological Attributes				
	a. Preservative effectiveness				
	b. CCI testing				
	c. Compatibility				
	Manufacture (names, locations, registration numbers and responsibilities of all sites involved)				
35.	Manufacturer(s)				
	a. Does the submission include descriptions and data, as appropriate, on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)? [Also applies to drug substance]				
36.	Batch Formula				
37.	Description of Manufacturing Process and Controls				
38.	Controls of Critical Steps and Intermediates				
39.	Process Validation and/or Evaluation				
	a. Process validation protocols and reports (in English or translated into English) including validation of all critical product manufacturing steps				
	b. Filter validation				
	c. Component, container, closure depyrogenation and sterilization validation				
	d. Validation of aseptic processing (media simulations)				

#	Item	Yes	No	N/A	Comments
	e. Lyophilizer sterilization validation				
	f. Other needed validation data (example: hold times)				
	g. If the test or process is not specified by regulation, are data provided to show that the alternate test or process is equivalent (21 CFR 610.9) to that specified by regulation? For example:				
	i. LAL instead of rabbit pyrogen				
	ii. Sterility				
	h. Are the representative sample(s) of the product to be marketed lot numbers identified and are they available upon request? Does the submission contain summaries of the representative sample(s) test results?				
	Control of Excipients				
40.	Specifications				
41.	Analytical Procedures (name, dosage form)				
42.	Validation of Analytical Procedures				
43.	Justification of Specifications				
44.	Excipients of Human or Animal Origin				
45.	Novel Excipients				
	Control of Drug Product				
46.	Specifications to ensure safety, identity, purity, and potency of Drug Product				
47.	Analytical Procedures in sufficient details				
	a. SOPs for release tests				

#	Item	Yes	No	N/A	Comments
48.	Validation of Analytical Procedures (Reports including data for the analytical procedures used for testing the DP)				
	a. Batch Analyses				
	b. Characterization of Impurities				
	c. Justification of Specification				
49.	Reference Standards or Materials				
	Container Closure System (A description of the container closure system)				
50.	Specifications (vial, elastomer, drawings)				
51.	Materials of construction				
52.	Suitability				
53.	Leachables and extractables				
54.	Container Closure Integrity (CCI)				
	Stability				
55.	Stability Summary and Conclusions				
56.	Post-approval Protocol and Commitment				
57.	Real-time Stability Data				
	a. Protocol				
	b. Results (data)				
	c. Method validation reports				
58.	Are data provided for the stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for the product assessment?				

#	Item	Yes	No	N/A	Comments
59.	Are stability data provided to support unique presentations? (i.e., hold time between (cell) preparation and administration when antigens are mixed with adjuvant prior to administrations; multidose vials between first and last vaccination draw; shipping)				
	Facilities and Equipment				
60.	Environmental Monitoring Program				
61.	Manufacturing flow; adjacent areas				
62.	Other products in facility				
63.	Equipment dedication, preparation, sterilization and storage				
64.	Procedures and design features to prevent contamination and cross-contamination				
65.	General description of water and HVAC systems, summary of validation/qualification, description of routine monitoring program				
66.	General description of computer systems which control critical manufacturing processes, including software validation and change control of automated systems				
67.	Are floor diagrams that address the flow of the manufacturing process for the drug substance and drug product?				

#	Item	Yes	No	N/A	Comments
68.	Does the submission include a description of precautions taken to prevent product contamination and cross-contamination, including identification of other products using the same manufacturing areas and equipment?				
	Adventitious Agents Safety Evaluation				
69.	Microbial contamination				
70.	Sterility				
71.	Avoidance and control procedures				
72.	Other materials of biological origin				
73.	BSE/TSE evaluation of materials used in manufacturing				
74.	Viral testing of unprocessed bulk (e.g., viral clearance)				
75.	Bioburden Testing at appropriate stages of production				
76.	Viral clearance studies				
77.	Cell line qualification				
78.	HCT/Ps Donor Testing and Screening				
79.	Novel excipients				
80.	USA Regional Information				
81.	Executed batch records (for DS and DP)				
82.	Method validation package				
83.	Comparability Protocols				
	a. Dosing & dosage, shelf-life evaluation, formulation, comparability assessment				
	b. Process comparability assessment, protocol, and report				
	c. Facility, equipment and container closure				
84.	Lot Release Protocol (LRP) template				
85.	Literature References				

#	Item	Yes	No	N/A	Comments
	Pre-Clinical				
86.	Animal studies to support safety and/or effectiveness of the vaccine				
	a. Immunogenicity				
	b. Virus shedding				
	c. Challenge				
	d. Biodistribution and integration				
	Clinical				
87.	Serology and virus detection assays to support clinical studies				
	a. SOP or method for the assay, including sample preparation, storage, shipping				
	b. Assay validation				
	c. Information on the laboratory where the assay is validated and routinely performed for sample evaluation				
	Combination Products				
88.	Is the product a combination product, combined with a delivery, scaffold, or other device?				
89.	Are one or more of the constituent parts under review by a different Center?				
	Companion Diagnostics				
90.	Is the product intended for use with an in vitro companion diagnostic device(s)?				
	Adjuvants				
91.	Description and composition of diluent and other components of the adjuvant				

Pharmacovigilance 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.

	Filing Checklist	Yes	No	NA	Comments
1.	Has the applicant submitted a post-marketing pharmacovigilance plan containing a safety specification and risk management plan?			N/A	
2.	If the pharmacovigilance plan proposes any new targeted postmarket observational safety studies, has the applicant submitted the accompanying concept protocols?				
3.	If the pharmacovigilance plan proposes any new REMS, has the applicant submitted the supporting REMS materials in the file?				

Statistical Filing Review 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.

	Filing Checklist	Yes	No	N/A	Comments
I.	**Is the index sufficient to locate all reports and data sets**				
II.	**Study Reports and related information**				
a.	Complete Study Reports are provided				
1)	All protocols and amendments are included				
2)	Statistical analysis plan (SAP) and amendments are included				
3)	Case report forms (CRFs) are included				
4)	Prespecified primary/critical analysis results are presented				
	Integrated summary of efficacy is provided				
c.	Integrated summary of safety is provided				
d.	Other studies and information (e.g., assay-related documentation and reports)				
e.	References				
III.	**Data Sets and Analysis Programs**				
a.	Data sets for all relevant studies are provided and readable, specifically:				
1.	Raw clinical datasets (e.g., SDTM)				
2.	Data dictionary				
3.	Analysis data sets (e.g., ADaM)				
4.	Analysis programs and descriptions				
b.	Data sets for integrated analysis if necessary				

BIMO Filing Review 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.

Items Required for Review and Assessment of BIMO file-able / Not file-able	Yes	No (Explain in Comments)	Comments
Complete listing of all clinical studies submitted in support of the Marketing Application			
Complete listing of all study sites for all clinical studies submitted, identified by: • Clinical Investigator name • Address • Telephone number • Study site number/other unique site identifier			
Clinical protocol(s) for all clinical studies submitted, including each of the corresponding study reports			
Clinical study data generated by each site for all clinical studies submitted, presented in a verifiable format (line listings/datasets) identifiable by individual study site and individual subjects within each dataset. **Example data tables**: • Protocol Violations/Deviations • Adverse Events • Demographics • Data specific to submission type and study conducted including all study endpoints			

Clinical Pharmacology Filing Review 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.

Format/Organization/Legibility

	Format/Organization/Legibility	YES	NO	NA	Comment
2.	Is the clinical pharmacology section organized in a manner to allow substantive review to begin?				
3.	Is the clinical pharmacology 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 and hyperlinks adequate)?				
5.	Are all documents submitted in English or are English translations provided when necessary?				
6.	Is the clinical pharmacology section legible so that substantive review can begin? (i.e., check for scanned pages or font size and type that are difficult or impossible to read)				

Summaries

	Summaries	YES	NO	NA	Comment
8.	Has the applicant submitted the clinical pharmacology overview?				

Dose

	Dose	YES	NO	NA	Comment
9.	Has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies), if applicable?				

Other Studies

	Other Studies	YES	NO	NA	Comment
10.	If applicable, has the applicant submitted all special studies/data (including pooled data analyses) requested by the Division during pre-submission discussions?				

Datasets

	Datasets	YES	NO	NA	Comment
11.	Has the applicant submitted individual subject concentration-time data and plots based on these data?				
12.	Has the applicant submitted individual subject PK data and arithmetic mean and standard deviation?				
13.	Is the age stratification, sample size, blood sampling scheme, and method of PK analysis in pediatrics acceptable?				
14.	Based on the pediatric PK study has the applicant submitted appropriate dosing recommendations for specific age groups?				

Return to Appendix