SOPP 8217: Administrative Processing and Review Management Procedures for Investigational New Drug Applications

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I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide for the Center for Biologics Evaluation and Research (CBER) staff to use for the administrative processing and review management procedures of Investigational New Drug Applications (INDs).

II. Scope

A. This SOPP applies to INDs received by CBER, including INDs for expanded access, except for individual emergency use requests. For policy and procedures regarding individual emergency use requests, see *Job Aid 851.07: Expanded Access INDs, Individual Emergency Use Requests*.

B. This SOPP does not address the specific content of scientific reviews.

III. Background

A. The Federal Food, Drug, and Cosmetic Act (FD&C Act), Section 505 requires a drug or biologic to be approved for marketing by the Food and Drug Administration (FDA) before it can be transported or distributed across state lines. An IND is a request from a sponsor to FDA for an exemption from this legal requirement. INDs are used for clinical studies to collect safety and efficacy information to support marketing applications for biologic and drug products or for medical research. INDs are also used under the expanded access provisions found in 21 CFR 312 Subpart I for treating patient(s) with an immediately life-threatening condition or serious disease or condition outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

B. In addition to federal laws, INDs are subject to regulations, including but not limited to, 21 CFR 312, 50, 54, 56, and 58. These regulations are intended to protect the rights, safety, and welfare of human subjects participating in clinical trials; to ensure the quality and integrity of clinical trial data; and to facilitate the availability of new medical products to the public.

C. This SOPP is a part of CBER's Managed Review Process (MRP). The goal of the MRP is to provide a quality and efficient process for all applications and submissions related to medical products regulated by CBER. The MRP includes the review process for the investigational phase which builds the foundation necessary to demonstrate safety, efficacy, and capability of consistent manufacture of drug or biological products. Timely and quality review of IND applications with appropriate feedback from and to sponsors enhances efficiencies via collaboration between CBER and sponsors throughout the drug development process, improves the quality of marketing applications, and allows more efficient review of marketing applications.

IV. Definitions

A. Commercial IND - An IND for an investigational drug or biological product intended to be eventually commercialized through the marketing application process.

B. Research/Non-Commercial IND - An investigational product for research or treatment purposes that is not intended to support commercialization at a later stage. If the sponsor initially submits a non-commercial/research IND, then submits either a phase 2 or phase 3 study protocol, the IND will then be considered a commercial IND unless the sponsor can justify that the phase 2 or phase 3 protocols are solely for research purposes and FDA agrees with the justification. (Per Form FDA 1571 instructions)

C. Clinical Investigation or Clinical Study or Clinical Trial - An experiment in which a drug is administered, dispensed, or used involving one or more human

subjects. For the purposes of this SOPP, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice (21 CFR 312.3(b)).

D. **Expanded Access IND** - A request to use an investigational medical product to diagnose, monitor, or treat a serious or immediately life-threatening disease or condition when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition. There are three categories of expanded access INDs: individual patient, including individual non-emergency and individual emergency use, intermediate-size patient populations, and treatment use (21 CFR 312, Subpart I).

E. **Human Subject** - An individual who participates in a clinical investigation, either as a recipient of an investigational new drug or as a control. Subject may be a healthy human or a patient with a disease or condition (21 CFR 312.3(b)) (21 CFR 50.3(g)).

F. **IND Amendment** - Additional information submitted to an IND to clarify, revise, or modify previously submitted information.

G. **Independent Ethics Committee (IEC)** - A review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection. An institutional review board, as defined in 21 CFR 56.102(g), is one type of IEC. (21CFR 312.3(b))

H. **Institutional Review Board (IRB)** - Any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the FD&C Act (21 CFR 56.102(g)).

I. **Investigational New Drug** - A drug or biological product that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes (21 CFR 312.3(b)).

J. **Investigational New Drug Application (IND)** - A request from a sponsor to FDA seeking permission to use an unapproved drug or biological product for the purpose of clinical investigation or clinical treatment.

K. **Investigator** - An individual who conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event that an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team (21 CFR 312.3(b)).

L. Sponsor - A person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators (21 CFR 312.3(b)).

M. Sponsor-Investigator - An individual who initiates and conducts an investigation and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator include both those applicable to an investigator and a sponsor (21 CFR 312.3(b)).

V. Policy

A. The procedures in this SOPP are not inclusive of all detailed procedures for INDs. This SOPP is to be used with applicable regulations, guidances, SOPPs, and job aids (JAs). IND review procedures include many specific topics. CBER staff will follow the specific requirements for a given topic in addition to the general requirements when managing INDs. The different sections of this SOPP are to be used seamlessly in conjunction with each other. For example, for an IND with a breakthrough therapy designation, reviewers will follow the procedures for such designation, and the general procedures for INDs.

B. Requirements for electronic submissions

1. Under Section 745A(a) of the FD&C Act, sponsors of commercial INDs and all subsequent amendments are required to submit information electronically in the appropriate FDA required electronic Common Technical Document (eCTD) and submit standardized study data for certain applications, including INDs. Refer to the following guidances:

a. *Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act.*

b. *Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications.*

c. *Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Standardized Study Data.*

d. *Guidance for Industry: Providing Regulatory Submissions in Electronic Format: IND Safety Reports.*

2. IND sponsors should request a submission tracking number (STN) from CBER prior to an eCTD submission. Refer to *SOPP 8117: Issuing Tracking Numbers in Advance of Electronic Submissions in eCTD Format.*

3. While non-commercial/research IND sponsors are exempt from the requirements for electronic submissions, they are encouraged to submit electronically using the eCTD format. For information regarding submission of eCTD exempt applications, refer to *SOPP 8110: Submission of Regulatory Applications - Exempt from eCTD Requirements* and *Guidance for Industry: Providing Regulatory Submissions in Alternate Electronic Format.*

4. CBER accepts formal submissions via email for individual patient INDs under Expanded Access provisions of 21 CFR 312.310. Refer to *SOPP 8119: Use of Email for Regulatory Communications*.

C. The content and format of any IND submission is expected to be complete and well-organized per 21 CFR 312. Further, per 21 CFR 312.23(a)(11), FDA can request any other relevant information needed for review of INDs.

The original IND submission must include information required per 21 CFR 312.23 and /or in 21 CFR 312 Subpart I for expanded access requests. Include all applicable FDA Forms as listed below. These forms can be located at *https://www.fda.gov/about-fda/reports-manuals-forms/forms*.

1. *Form FDA 1571: Investigational New Drug Application*

   Note: For individual patient expanded access INDs, a licensed physician may use *Form FDA 3926: Individual Patient Expanded Access IND* instead of Form FDA 1571. Information about Form FDA 3926 can be found in *Guidance for Industry: Individual Patient Expanded Access Applications: Form FDA 3926.*

2. *Form FDA 1572: Statement of Investigator. Refer to Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions – Statement of Investigator (Form FDA 1572)*

3. *Form FDA 3674: Certification of Compliance Under 42 U.S.C. § 282(j)(5)(B), with Requirements for Clinical Trials.gov Data Bank*

Note: Form FDA 3454 and Form FDA 3455 are not required to be submitted in INDs. However, IND sponsors are required to obtain clinical investigator financial information before allowing the investigators to participate in the study. (21 CFR 312.53). IND sponsors are also required to maintain and update records regarding clinical investigator's financial information. Refer to Guidance: *Financial Disclosure by Clinical Investigators.*

It is recommended that sponsors include the informed consent documents (ICD) in their IND submissions, because ICDs help to assess the safety and human subject's protection when evaluating whether a clinical study may proceed. If a sponsor does not submit an ICD as part of its IND submission, CBER can request ICDs from sponsors per 21 CFR 312.23(a)(11). ICDs must comply with the requirements found in 21 CFR 50. It must contain information to allow the subject to make an informed decision about participation in a clinical investigation covering all procedures as well as the information about the investigational product used in the clinical study. CBER's review of the ICDs does not substitute for the responsibility or authority of the IRB /IEC for ICDs.

A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under 21 CFR 50.24. (21 CFR 312.20(c))

IND amendments that contain different types of information that have mandated review timelines should be submitted separately. For example, an amendment requesting fast track designation should be submitted separately from an amendment for a pediatric study plan. Form FDA 1571 and the cover letter should clearly specify the type of information that is being submitted in the amendment.

D. CBER staff are responsible for protecting confidential information, such as proprietary information, trade secrets, company confidential information, and patient privacy information.

1. CBER staff will follow policy and procedures in *SOPP 8119: Use of Email for Regulatory Communications* for secure email communication.

2. CBER reviewers cannot send IND submissions back to the sponsor or to any external requester, even if the requester is the same person who submitted the information. Any external stakeholder seeking information submitted to CBER must submit a Freedom of Information (FOI) request to FDA. For FOI policy and procedures, refer to *SOPP 6408: Protecting Non-Public Information and the Freedom of Information Act*.

3. Information received from a third party (e.g., proprietary information from a contract manufacturer) must be submitted in a cross-referenced master file. Refer to *SOPP 8301: Receipt and Processing of Master Files* for pertinent information regarding master files. Only information from the sponsor may be added to the IND file.

4. The sponsor ordinarily is not required to resubmit information previously submitted but may incorporate the information by reference. A reference to information submitted to CBER by a person other than the sponsor is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information. (21 CFR 312.23(b)). Sponsors may not reference an IND in terminal status.

a. CBER staff will not terminate an inactive IND that has been inactive for 5 years or more if the inactive IND is already being cross-referenced.

E. Review staff will follow applicable law, regulations, guidances, policies, procedures, and utilize available reviewer templates that have been approved specifically for assigned areas of responsibility.

F. CBER review staff will adhere to the *Guidance for Industry and Review Staff: Best Practices for Communication Between IND Sponsors and FDA During Drug Development* for effective and timely interactive communication with sponsors.

G. All communications, including telephone calls and other informal communications, are to be entered into the appropriate regulatory system in a timely fashion. All documents should be entered into the appropriate regulatory systems. All letters issued by CBER must use the most recently approved letter template (available on the Letter Templates site on CBER's Review Resources SharePoint hub). Defined dates used on CBER correspondence and entered into CBER systems are described in *JA 820.02: Dating of CBER Correspondence*.

H. IND review timelines established by statute and/or regulation apply firmly to CBER's IND process. Certain types of IND submissions (e.g., an IND amendment for a new protocol under an active IND) do not have statutory or regulatory timelines but may have CBER internal targeted timelines. Refer to Appendix A of this SOPP and Regulatory Reference *R 851.03: Review Timelines and Routing Triage for INDs and IND-Related Submissions* for IND review timelines. Goal dates are in calendar days unless stated otherwise.

I. Review Team Members must keep management up to date of any significant review issues.

J. Unless patients are exposed to immediate and serious risk, CBER will attempt to discuss and satisfactorily resolve potential hold-related review issues with the sponsor **before** issuing a clinical hold order. Refer to *SOPP 8201:Administrative Processing of Clinical Holds for Investigational New Drug Applications* for detailed information regarding CBER's policies and procedures on clinical hold.

K. CBER will manage INDs to ensure that IND statuses in the regulatory system are accurate and timely updated. CBER staff will use this SOPP in conjunction with *R 850.01: IRA Terminal Statuses and Communication Requirements.*

1. CBER will manage INDs to ensure that INDs with terminal status are placed in the terminal status in a timely manner. INDs that are left in a non-terminal status when in fact they should be in a terminal status cause unnecessary administrative work and distort CBER's workload tracking and reporting.

2. Terminal statuses include, but are not limited to, INDs that are exempted, withdrawn, terminated or transferred to another FDA Center. See *R 850.01: IRA Terminal Statuses and Communication Requirements* for definitions.

3. The process of placing an IND in a terminal status may be initiated in response to a request from the sponsor, or/and by FDA as a result of failure to submit required safety and periodic reports, an extended inactive state, a safety issue or other reasons stated in 21 CFR 312.44.

4. Prior to placing an IND in terminal status, the IND file should be updated with all relevant documentation including reviews and correspondence, i.e., all relevant documentation has been entered into the appropriate regulatory systems.

5. INDs placed in a terminal status are documented by an IND Status changing communication (e.g., letter, email, or telecon), when applicable, or by a memorandum to the file.

6. Submissions from sponsors are not expected to be received to an IND in a terminal status. No sponsor's submission will revise a terminal IND status, except for a request for reinstatement (in rare circumstances) of a terminated IND. INDs in terminal statuses may not be cross-referenced.

7. The IND status cannot be changed once placed in terminal status (except in rare circumstances when there is a request for reinstatement).

VI. Responsibilities

A. Branch Chief – ensures that the overall content of reviews is appropriate, all deadlines are met. Reviews and approves employee's review documents and other submission documents per CBER policies and procedures. Keeps Division Director informed of important issues related to IND reviews.

B. Discipline Reviewer – performs review of assigned areas of the submission, participates in relevant meetings, provides letter ready comments for conveyance to the sponsor, assures their review has been documented; and enter reviews and any other documentation into the appropriate regulatory system. Identifies and informs RPM the need for inter-center and intra-center consults. Works closely with the RPM in executing these duties.

C. Division Director – stays informed of important issues related to IND reviews; addresses specific issues brought to his or her attention through the discipline or division management chain; consults with the Office Director, the Associate Director for Review Management (ADRM), the Center Director, and other appropriate groups, as necessary.

D. **Document Control Center (DCC)** – receives, digital images (if applicable), and processes non-eCTD submissions, including loading electronic applications into CBER's electronic repository (CER), and notifies office and RIB via the electronic load notification.

E. **Electronic Submission Program Manager (ESPM) / DCC –** responsible for the receipt, processing, and loading of regulatory submissions for reviewer access. Serves as primary contact to sponsors and stakeholders for guidance and support to resolve ingest validation, technical rejection, and submission access issues.

F. **Office of Regulatory Operations (ORO), Division of Informatics (DI), Regulatory Information Branch (RIB)** – issues pre-assigned IND numbers for electronic submissions; works with the RPM for IND submission characterization in the regulatory system; works with review offices for data quality; and generates IND review performance reports.

G. **Regulatory Information Specialist (RIS)** – provides administrative support for IND related matters.

H. **Regulatory Project Manager (RPM) –** responsible for the overall management of IND processing and review.

   1. Serves as the primary point of contact with sponsors and stakeholders.

   2. Works closely with the discipline review team, ensures the review team is kept up to date on all aspects of IND review, brings scientific and regulatory issues to the attention of management, works with review team to facilitate and ensure resolution and consensus of review issues especially when issues cross disciplines.

   3. Serves as a resource for regulatory knowledge, FDA and Center policies, procedures, and business process documents such as checklists and templates.

   4. Schedules and manages internal and external review meetings, presents regulatory issues identified during the review and options for regulatory action or resolution.

   5. Drafts key regulatory decision communications, such as clinical hold letter consistent with FDA and CBER policies, procedures, and current templates.

   6. Captures review team communications and ensures that the appropriate regulatory systems are updated with the correct information, and files are administratively complete.

7. Performs quality control checks. Ensures all sections of the IND have been assigned for review. Ensures regulatory and administrative actions including inter-center consults are completed on time and may identify when consults are needed. Notifies management when timelines are not met.

8. Contacts RIB for any questions regarding IND status, including characterization and data entry in regulatory systems.

I. Regulatory Project Management Supervisor (RPM Supervisor) – supervises and manages RPMs for INDs, such as assignment, ensuring completion of RPM tasks, and problem-solving of RPM-related issues.

J. Team Lead – if applicable, makes work assignments when delegated; leads the IND review and ensures resolution of scientific and regulatory issues in concert with management. Specific responsibilities include ensuring all sections of the IND have been assigned for review, and review decisions are scientifically sound and consistent with current law, regulations, policies and procedures; drafting key regulatory decision communications, such as clinical hold letter comments; bringing scientific issues to the attention of management and facilitating resolution and consensus. The team lead works closely with the RPM in executing these duties.

VII. Procedures

Note:

Each step in the procedure section is chronologically listed where practicable. It is permissible and may be necessary to accomplish steps out of sequence, when appropriate.

Review assessment and documentation start when the IND application is received and continues throughout the life cycle of the IND.

A. Receipt, Processing, Routing and Assignment of Original IND

1. Receive, digitally image (if applicable), process, and load into the CER. Notify the appropriate review office and RIB through CER load notification. **[DCC, ESPM**] **Note:** The IND review clock starts when the application (including applications transferred from other FDA centers to CBER) has been logged by DCC with a CBER receipt date.

2. Monitor for load notifications and inform the appropriate RPM supervisor upon notification of IND receipt. **[RIS, RPM Supervisor]**

3. Determine if the IND is non eCTD and belongs to CBER. If an IND belonging to another FDA Center is misdirected to CBER, DCC will transfer the IND to the correct jurisdictional Center per DCC Procedure Guide 2: *Transfer of*

Investigational Related Applications (IRAs) to Another Center. If misdirected submission is eCTD, DCC will forward to ESPM for technical rejection. **[RPM Supervisor, RIB, DCC, ESPM]**

4. Assign an RPM. **[RPM Supervisor]**

5. Characterize the IND submission. Ensure that all data are entered, and all necessary fields are completed in the appropriate regulatory system. **[RIB, RPM]**

6. Conduct a preliminary review; ensure the elements required for Form FDA 1571 under 21 CFR 312.23(a)(1) are included in the submission, e.g., that the Form FDA 1571 is complete and signed. Ensure other required forms such as Form FDA 3674 are included in the submission and the forms are completed with required information. **[RPM]**

    a. Contact the sponsor and request the missing information related to Form FDA 1571 and other required forms.

7. Ensure that the characterization of the IND is correct and complete by conducting a quality check in the appropriate systems. **[RPM]**

8. Identify other submissions cross-referenced to the IND; enter the information into the appropriate regulatory system. **[RIB, RPM]**

    a. Identify any submissions referred to by the sponsor (both on Form FDA 1571 and within application), for example, a previous pre-IND meeting, an INTERACT meeting or a letter of authorization.

    b. Ensure that a check is made for pre-submissions and cross-references are listed for the IND in the appropriate regulatory system. Ensure the pre-submission is closed once the IND is received. Refer to SOPP 8114: Administrative Processing of Documents Received Prior to Submitting Investigational or Marketing Applications (Pre-Application).

    c. Ensure that any referenced master files are available to the appropriate reviewers as necessary. If master files are located in another FDA Center, contact CBER's Product Jurisdiction Officer in the office of the Center Director to facilitate gaining access to the files. Refer to SOPP 8301: Receipt and Processing Master Files for information on routing master files for review.

    d. Ensure that the cross-referenced INDs are not in terminal status. If cross-referenced INDs are in terminal status, notify the sponsor that terminated INDs may not be cross-referenced, because the sponsor of a terminated IND has no obligation to submit reports or to update the file.

9. Notify appropriate supervisors of receipt of the application, request assignment or confirm review team members, including the following, as applicable: **[RPM]**

    a. Primary Reviewer (product office)

    b. Clinical Reviewer (product office)

    c. Clinical Pharmacology Reviewer (product office)

    d. Pharmacology/Toxicology Reviewer (product office)

    e. Chemistry, Manufacturing and Controls (CMC) Reviewer (product office)

    f. Bioinformatics Reviewer (product office)

    g. Biostatistics/Pharmacovigilance Reviewer (Office of Biostatistics and Pharmacovigilence (OBPV))

    h. Digital Health Technology (DHT) Reviewer (OBPV)

    i. Real World Evidence (RWE) Reviewer (OBPV)

    j. Benefit-Risk Assessment Reviewer (OBPV)

    k. Labeling, Proprietary Name Reviewer (Product Office and Advertising and Promotional Labeling Branch (APLB), Division of Case Management (DCM), Office of Compliance and Biologics Quality (OCBQ))

    l. Reviewer(s) from OCBQ:

        i. Bioresearch Monitoring Program (BIMO) Representative

        ii. Division of Manufacturing and Product Quality (DMPQ) Representative

    m. Preclinical Pharmacology Reviewer

    n. Consult Reviewer

10. Assign review team members; notify RPM. **[Supervisor]**

11. Ensure that all assigned review team members are entered into the appropriate regulatory system. Ensure the IND is correctly routed in the regulatory system to the review team and that any consult reviewer(s) have access to the submission. **[RPM]**

12. Send a notification, including review plan and review schedule, to all review team members and their supervisors, including consult reviewers and their supervisors, as appropriate. **[RPM]**

    a. Identify all regulatory tracks/topics within the IND and their respective timelines that need to be met (e.g., request for designation of breakthrough therapy has a different timeline than the original IND submission). Ensure the review plan and review schedule meet the specific requirements and timelines for the specific regulatory topics. Refer to *Appendix A* and *R 851.03*: *Review Timelines and Routing Triage for INDs and IND-Related Submissions* for detailed review timelines.

13. Ensure that an acknowledgement of receipt letter is issued, is entered in the appropriate regulatory system. **[RPM, RIS]**

    Note: *21 CFR 312.40* requires that FDA notify the sponsor in writing of the date when it receives an IND.

B. Review of Original INDs

1. Initiate review. Verify that the submission contains complete information needed for IND review. **[Review Team Members, RPM]**

2. Discuss with the sponsor, as early as possible and practical, issues that may be resolvable and could prevent a clinical hold or partial hold. As part of the communication and in alignment with the *Guidance for Industry and Review Staff: Best Practices for Communication Between IND Sponsors and FDA During Drug Development*, the sponsor should provide an estimated response time. **[RPM, Appropriate Review Team Member(s)]**

    a. As resources allow, CBER will aim to request additional information via email or telecon (e.g., for complex potential hold issues) no later than day 21 following receipt of IND).

    b. Provide the sponsor with a requested response date.

    Note: CBER requests that sponsors respond by the requested response date to allow CBER time to review within 30 days.

    c. Document and enter the communication in the appropriate regulatory system.

3. Receive, process, route and assign solicited amendments according to procedures for IND Amendments (see Section VII-C of this SOPP). **[ESPM, DCC, RIB, RPM]**

4. Determine and verify the need for consults following the procedures and timelines in *SOPP 8001.5: Inter-Center Consultative Review Process*. **[Review Team Members]**

5. Make consult assignment(s) if needed in the appropriate regulatory system, notify consultant(s) of the assignment and due date. **[RPM]**

    a. Refer to *SOPP 8001.5: Inter-Center Consultative Review Process* for inter-center consult request (ICCR) procedures.

    Note: Follow mandatory and internal timelines in SOPP 8001.5 when processing consults. There are target dates for completing the ICCR form and for identifying the consult center lead.

    b. Consulting among offices within CBER is processed by emailing the appropriate person in the consulting office/division.

6. Schedule and conduct internal meetings/discussions as needed**. [RPM, Review team members, Team Lead, Branch Chief]**

7. Schedule, prepare, and conduct informal meetings/discussions with sponsors as needed. For example, per 21 CFR 312.42(c) reviewers will attempt to discuss and resolve potential clinical hold issues. **[RPM, Review Team Members, Team Lead, Branch Chief]**

8. Review IND and solicited amendments; provide responses as needed. **Note:** Be aware of other submissions that are cross-referenced to the IND, such as a pre-IND meeting. **[Review Team Members]**

    a. Ensure review meets specific requirements and timelines for specific submission types / topics, as applicable. Refer to the respective SOPP, Appendix A of this SOPP, *and R 851.03: Review Timelines and Routing Triage for INDs and IND-Related Submissions*.

9. Determine if issues are identified that may justify imposing a clinical hold. **[Review Team Members]**

    a. Follow the policy and procedures for clinical holds in *SOPP 8201: Administrative Processing of Clinical Holds for Investigational New Drug Applications*. **[RPM, Review Team Members, Team Lead, Branch Chief, Division Director]**

    Note: An IND goes into effect 30 calendar days after FDA receives the IND, unless FDA notifies the sponsor that the clinical investigations described in the IND are subject to a clinical hold, or on earlier notification by FDA that the clinical investigations may begin. (21 CFR 312.40(b)). However, an IND involving an exception from informed consent requirements for emergency

research under 21 CFR 50.24 is not permitted to proceed without the prior written authorization from FDA. CBER will provide a written determination within 30 days after CBER receives the IND involving exception from informed consent requirements for emergency research. (21 CFR 312.20(c)). See *SOPP 8209: Process for Review and Monitoring of Applications Involving Clinical Studies under Provisions of 21 CFR 50.24: Exception from Informed Consent Requirements for Emergency Research.*

10. When necessary, communicate with sponsors about issues not related to clinical hold. Document the communication in the appropriate regulatory system and ensure the correct communication codes are used in the regulatory system. **[RPM]**

11. Upload the completed review memo into the appropriate regulatory system. Ensure supervisory concurrence when necessary. **[Review Team Members]**

12. After review completion, move consultants external to the review office to the review history in the appropriate regulatory systems. Issue a new consult request for IND amendments, as necessary. **[RPM]**

C. IND Amendments

1. Receipt, Processing, Routing, and Assignment

a. Receive, digitally image (if applicable), process, and load IND amendments into the CER. **[ESPM, DCC]**

b. Notify the appropriate Office and RIB through the CER load notification. The IND amendment review clock, when applicable, starts when the IND application is logged into DCC system with a CBER receipt date for the IND amendment. **[ESPM, DCC]**

c. Monitor for notifications of receipt of IND amendments. **[RPM, RIB]**

d. Ensure that all data, including characteristic codes, the short summary, and all necessary fields are complete in the appropriate regulatory system. **[RIB, RPM]**

e. Route the amendment in the appropriate regulatory system to the relevant review team members. **[RPM]**

i. Inform DMPQ management via email and request reviewer assignment if DMPQ review is needed. **[RPM]**

f. If applicable, ensure that an acknowledgement of receipt letter is issued (refer to *R 851.03: Review Timelines and Routing Triage for INDs and IND*

Related Submissions), entered in the appropriate regulatory system. **[RPM]**

2. Review of IND Amendment

a. Initiate the review by ensuring the amendment contains the necessary elements and contents. **[Review Team Members, RPM]**

b. Establish and confirm a review plan and schedule as applicable, inform all review members of this schedule. **[RPM]**

i. Ensure that the review plan and schedule meet the specific requirements and timelines for specific submission types/topics. For IND review timelines, refer to Appendix A of this SOPP *and R 851.03: Review Timelines and Routing Triage for INDs and IND-Related Submissions*.

c. Determine if a consult is needed; enter the consult assignment in the appropriate regulatory system, and notify the consultant of the assignment and due date. **[RPM, Review Team Members]**

i. Refer to *SOPP 8001.5: Inter-Center Consultative Review Process* for ICCR procedures.

Note: Follow mandatory and internal timelines in *SOPP 8001.5* when processing consults. There are target dates for completing ICCR form and for identifying consult center lead.

ii. Consulting among offices within CBER is processed by emailing the appropriate person in the consulting office / division.

d. Review IND amendments and the solicited information. Consider the status of the original IND while reviewing each amendment. Determine the impact of the amendment on the original IND and appropriate subsequent actions needed. Provide a response as needed. **[Review Team Members]**

i. Conduct a review of amendments, determine if clinical hold is needed. Refer to 21 CFR 312 and *SOPP 8201: Administrative Processing of Clinical Holds for Investigational New Drug Applications*, for procedures related to clinical hold, continued clinical hold, or removing clinical hold. **[RPM, Review Team Members, and Division Director]**

ii. Ensure that the review meets specific requirements and timelines for specific submission types/topics, if applicable. Refer to the respective SOPP, Appendix A of this SOPP, and *R 851.03: Review Timelines and Routing Triage for INDs and IND-Related Submissions*.

e. Request additional information from the sponsor if necessary and enter the information request into the appropriate regulatory system. **[Review Team Members, RPM]**

f. Schedule, prepare, and conduct meetings with IND sponsors as needed. For formal meetings, refer to the policy and procedures in *SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products*. **[RIS, RPM, Review Team Members, Division Director]**

g. Enter the completed review memo into the appropriate regulatory system; ensure that the correct communication codes are used and ensure that supervisory concurrence has been obtained when necessary. **[Review Team Members]**

h. After review completion, move consultants external to the review office to the review history in the appropriate regulatory systems. Issue a new consult request for IND amendments, as necessary. **[RPM]**

D. Managing Changes of IND Status

1. Clinical Hold and Removing of Clinical Hold (21 CFR 312.42)

a. Refer to *SOPP 8201: Administrative Processing of Clinical Hold for Investigational New Drug Applications.* **[RPM]**

b. Ensure the correct communication code and reason(s) for hold are entered into the regulatory system to reflect the correct IND status**. [RPM]**

2. Exemption of IND (21 CFR 312.2)

a. Review sponsor's request for IND exemption and determine if the IND may be considered exempt, under the criteria set forth in 21 CFR 312.2. **[RPM, Review Team Members]**

Note:

i. An exemption request may also be considered with the original IND.

ii. CBER will not accept an IND, or amendments, for review if the IND is exempted within the meaning of 21 CFR 312.2.

iii. Refer to 21 CFR 312.2, and *Guidance for Clinical Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND*

b. Draft, route, review, sign, and send the notification letter to sponsor regarding the decision of whether the IND can be exempted. **[RIB, RPM, Review Team Members, Division Director]**

c. Upload the notification letter to the appropriate regulatory system. Ensure that the correct communication code is entered into the regulatory system to update the status in the regulatory system. **[RPM]**

3. Inactivation of IND (21 CFR 312.45)

a. Identify INDs that potentially meet the criteria for inactivation per 21 CFR 312.45 or receive sponsor's request for inactivation for INDs that meet the inactivation criteria under 21 CFR 312.45. If inactivation is requested by a sponsor, go directly to step d of this section. **[RIB, RPM]**

Note: Gene therapy and xeno-transplantation INDs may require long-term follow-up and, thus, may not be candidates for inactivation. The additional considerations are described in the *Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products*.

b. Draft, route, review, sign, and send IND pre-inactivation notification to the sponsor if no subjects are entered into clinical studies for a period of 2 years or more under an IND, or if all investigations under an IND remain on clinical hold for 1 year or more, per 21 CFR 312.45. Ensure that the correct communication code is entered into the appropriate regulatory system. **[RIB, RPM, Review Team Members]**

c. Review sponsor's response to the pre-inactivation letter and determine if the IND should be inactivated within 30 days after receiving the sponsor's response. **[RIB, RPM, Review Team Members]**

d. Draft, route, review, sign, and send the IND inactivation notification letter to the sponsor if the sponsor does not respond to the IND pre-inactivation letter within 30 calendar days of receipt of the letter, or the sponsor fails to justify within 30 days the reason(s) why the IND should continue to remain active, or if the inactivation request is made by the sponsor and the sponsor's request meets the inactivation criteria identified under 21 CFR 312.45. **[RIB, RPM, Review Team Members]**

e. Upload the inactivation notification letter to the appropriate regulatory system. Ensure that the correct communication code is entered into the regulatory system to update the IND status in the regulatory system. **[RPM]**

4. Reactivation of IND (21 CFR 312.45)

a. Receive IND reactivation request and reactivation protocol amendment from sponsor.

Note: Per 21 CFR 312.45(d), a sponsor who intends to resume clinical investigation under an IND placed on inactive status shall submit a protocol amendment containing information required under 21 CFR 312.30, including the proposed general investigational plan and appropriate protocols. **[RPM]**

b. Send acknowledgement of receipt letter to the sponsor. Upload the acknowledgement letter to the appropriate regulatory system. **[RPM]**

c. Skip step d and e, go to step f of this section, if the IND was on clinical hold/partial hold prior to inactivation.

d. Review IND reactivation request and protocol amendment **within 30 days of receipt** of such request, determine if the IND can be reactivated/allowed to proceed according to 21 CFR 312.45(d) and/or if the IND must be placed on clinical hold. **[RPM, Review Team Members]**

i. Refer to *SOPP 8201: Administrative Processing of Clinical Hold for Investigational New Drug Applications* for clinical hold procedures.

e. Communicate with sponsor as needed. Upload pertinent documents to the appropriate regulatory system. Ensure the correct communication code is entered into the regulatory system to reflect the correct IND status. **[RPM]**

f. If the IND was on clinical hold or partial hold prior to the inactivation of the IND, the reactivation request will change the IND status back to clinical hold or partial hold, depending on the status of the IND prior to inactivation. Follow *SOPP 8201: Administrative Processing of Clinical Hold for Investigational New Drug Applications* for clinical hold procedures. **[RPM, Review Team Members]**

5. Termination of IND (21 CFR 312.44, 312.45, 312.33)

a. Identify INDs that potentially meet criteria for termination, per criteria set in 21 CFR 312.44. **[RIB, RPM]**

i. Note: CBER staff will not terminate an inactive IND that has been inactive for 5 years or more if the inactive IND is being cross-referenced.

ii. Note: Once an IND is terminated, a new IND must be submitted if the product is subjected to clinical study again, except reinstated INDs (very rare exception).

iii. Note: Gene therapy and xeno-transplantation INDs may require long-term follow-up and, thus, may not be candidates for termination. The additional considerations prior to termination are described in the *Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products.*

b. If CBER concludes at any time that continuation of the investigation presents an immediate and substantial danger to the health of individuals, skip steps c and d regarding pretermination in this section, and proceed to the immediate termination steps below:

i. Draft, route, review and finalize immediate termination letter to the sponsor. **[RIB, RPM, Review Team Members, Branch Chief, Division Director]**

ii. Send the finalized immediate termination letter to the CBER Director for signature. **[RPM]**

iii. Send the immediate termination letter to sponsor. **[RPM]**

Note: An IND immediately terminated under 21 CFR 312.45(d) is subject to reinstatement by the CBER Director on the basis of additional submissions that eliminate such danger. If an IND is immediately terminated under 21 CFR 312.45(d), the agency will afford the sponsor an opportunity for a regulatory hearing under 21 CFR 16 on the question of whether the IND should be reinstated.

c. Draft, route, review, sign, and send an IND pre-termination notification to the sponsor about CBER's intent to place the IND on terminated status if the IND has remained on an inactive status for 5 years or more, per 21 CFR 312.45, or for termination based on deficiencies in the IND or in the conduct of an investigation under an IND, as set forth in 21 CFR 312.44. Upload the pre-termination notification letter to the appropriate regulatory system. **[RIB, RPM, Review Team Members, Branch Chief, Division Director]**

i. Prior to issuing a pre-termination letter, ensure that there is no cross-referencing to the inactive IND. If the inactivated IND is still being cross-referenced, do not continue the pre-termination process. **[RIB, RPM]**

ii. If the sponsor responds to CBER's pre-termination letter within 30 days and disagrees with CBER's reason(s) for termination, but CBER does not accept the sponsor's explanation or correction submitted, inform the sponsor in writing of the reason for the nonacceptance and provide the sponsor with an opportunity for a regulatory hearing under 21 CFR 16 regarding whether the IND should be terminated. The sponsor's

request for a regulatory hearing must be made within 10 days of sponsor's receipt of FDA's notification of nonacceptance.

d. Review sponsor's response to the pre-termination letter and determine if the IND should be terminated within 30 days after receiving the sponsor's response**. [RIB, RPM, Review Team Members]**

e. Draft, route, review, sign, and send the IND termination notification letter to the sponsor if the sponsor does not respond to the IND pre-termination letter in 30 calendar days or later after receipt of the letter, or the sponsor fails to justify within 30 days the reason(s) why the IND should not be terminated. **[RIB, RPM, Review Team Members]**

f. Upload the termination notification letter to the appropriate regulatory system. Ensure that all relevant documentation including written reviews and correspondence have been entered into the appropriate regulatory system prior to placing the IND in terminal status. Ensure that the correct communication code is entered into the regulatory system to reflect the correct IND status. **[RPM]**

6. Withdrawal of IND (21 CFR 312.38)

a. Review sponsor's request for IND withdrawal and determine if the IND may be withdrawn. **[RIB, RPM, Review Team Members]**

i. Note: Once an IND is withdrawn, a new IND must be submitted if the product is again subject to clinical study.

ii. Note: Gene therapy and xeno-transplantation INDs may require long-term follow-up and, thus, may not be candidates for withdrawal. The additional considerations prior to withdrawal are described in the *Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products.*

b. If the IND may be withdrawn, then draft, route, review, sign, and send the IND withdrawal acknowledgement notification letter to the sponsor. **[RIB, RPM, Review Team Members]**

c. Upload the withdrawal acknowledgement notification letter to the appropriate regulatory system. Ensure that the correct communication code is entered into the regulatory system to update the IND status in the appropriate regulatory system. **[RPM]**

VIII. Appendix

A. Statutory Review Timelines for INDs and IND-Related Submissions

IX. References

A. References below are CBER internal:

1. Document Control Center Procedures

a. DCC Procedure Guide 2: Transfer of Investigational Related Applications (IRAs) to Another Center

2. Regulatory Job Aids (JAs)

a. JA 820.02: Dating of CBER Correspondence

b. JA 851.07: Expanded Access INDs, Individual Emergency Use Requests

3. Regulatory References

a. R 810.04: Meeting Information

b. R 850.01: IRA Terminal Statuses and Communication Requirements

c. R 851.03: Review Timelines and Routing Triage for Investigational Drug Applications (INDs) and IND-Related Submissions

4. Standard Operating Policies and Procedures (SOPPs)

a. SOPP 6408: Protecting Non-public Information and the Freedom of Information Act

b. SOPP 8001.5: Inter-Center Consultative Review Process

c. SOPP 8209: Process for Review and Monitoring of Applications Involving Clinical Studies under Provisions of 21 CFR 50.24: Exception from Informed Consent Requirements for Emergency Research

B. References below can be found on the Internet:

1. Statues and Regulations

a. Code of Federal Regulations, Title 21

2. Guidance Documents

a. Guidance for Clinical Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs): Determining Whether Human Research Studies Can Be Conducted Without an IND

b. Guidance for Industry: Individual Patient Expanded Access Applications: Form FDA 3926

c. Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products.

d. Guidance for Industry: Providing Regulatory Submissions in Alternative Electronic Format

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

f. Guidance for Industry: Providing Regulatory Submissions in Electronic Format: IND Safety Reports

g. Guidance for Industry: Providing Regulatory Submissions In Electronic Format — Standardized Study Data

h. Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act

i. Guidance for Industry and Review Staff: Best Practices for Communication Between IND Sponsors and FDA During Drug Development

j. Draft Guidance: Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions Statement of Investigator (Form FDA 1572)

3. Standard Operating Policy and Procedures

a. SOPP 8110: Submission of Regulatory Applications – Exempt from eCTD Requirements

b. SOPP 8114: Administrative Processing of Documents Received Prior to Submitting Investigational or Marketing Applications (Pre-Application)

c. SOPP 8117: Issuing Tracking Numbers in Advance of Electronic Submissions in eCTD Format

d. SOPP 8119: Use of Email for Regulatory Communications

e. SOPP 8201: Administrative Processing of Clinical Holds for Investigational New Drug Applications

f. SOPP 8301: Receipt and Processing Master Files

4. FDA Forms

   a. Form FDA 1571: Investigational New Drug Application (IND)

   b. Form FDA 1572: Statement of Investigators

   c. Form FDA 3454: Certification: Financial Interests and Arrangements of Clinical Investigators

   d. Form FDA 3455: Disclosure: Financial Interests and Arrangements of Clinical Investigators

   e. Form FDA 3674: Certification of Compliance, under 42 U.S.C. , 282(j)(5)(B), with Requirements of ClinicalTrials.gov

   f. Form FDA 3926: Individual Patient Expanded Access Investigational New Drug Application (IND)

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Xiaoqiu Tang	Sonday Kelly, MS, RAC, PMP Director, DROP/ORO	July 5, 2024	5	Update to allow cross-referencing to inactive INDs; Reminder added to load all docs. in the regulatory systems before setting IND to terminal status; Move policy items from R 850.01; Incorporate ESP and ESPM; Add reference to QIDP per FDORA; Add reference to IND safety reporting. Remove Forms 3454 and 3455 from IND submission requirement.

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Rivers/Kelly/Tang/ Monser	Sonday Kelly, MS, RAC, PMP Director, DROP/ORO	December 15, 2023	4	Update to incorporate best practice for issuing IRs no later than day 21 for potential hold issues as resources allow and added additional reviewers to review team
Monser	N/A	February 27, 2023	3	Technical Update for 2023 CBER reorganization
Xiaoqiu Tang; Cherie Ward-Peralta	Darlene Martin, MS, PMP ORO/DROP Director (Acting)	September 28, 2022	2	Update for PDUFA VII
Xiaoqiu Tang and IND WG	Christopher Joneckis, PhD	February 10, 2022	1	First Issuance

SOPP 8217: Appendix A: Statutory Review Timeline for INDs and IND Related Submissions

Note:

- Unless specified otherwise, due dates are in calendar days. If the due date is on a weekend or holiday, the review and communication are due on the previous Friday or the working day before the holiday.
- Review clock starts on Day 1, the date of receipt of the respective review item or correspondence from sponsor. For example, the 30 day review clock for determining clinical hold starts when the IND or amendment is received by CBER.
- Use this Appendix in conjunction with the applicable regulations, guidances, SOPPs, JAs, Regulatory References and other business process documents, as appropriate.

Acronyms:

- BPCA: Best Pharmaceuticals for Children Act
- Cures Act: 21st Century Cures Act of 2016
- FDAAA: Food and Drug Administration Amendments Act of 2007
- FDAMA: The Food and Drug Administration Modernization Act of 1997
- FDARA: The FDA Reauthorization Act of 2017
- FDASIA: The Food and Drug Administration Safety and Innovation Act of 2012
- FDCA: The Federal Food, Drug, and Cosmetic Act
- FDORA: The Food and Drug Omnibus Reform Act of 2020
- PDUFA: Prescription Drug User Fee Amendments
- PSP: Pediatric Study Plan
- RMAT: Regenerative Medicine Advanced Therapy
- SPA: Special Protocol Assessment

Review Subject	Statutory Review Clock	Final Action or Response	Statutory Reference
Original IND	30 days	Hold or proceed telecon by day 30; Hold / May proceed (Advice) letter no later than 30 days after the initial notification telecon; Hold /May proceed letter no later than 30 days after	21 CFR 312.42

Review Subject	Statutory Review Clock	Final Action or Response	Statutory Reference
		receipt of complete response	
Treatment protocol submitted as IND amendment	30 days	Hold or proceed telecon by day 30; Hold / May proceed (Advice) letter no later than 30 days after the initial notification telecon; Hold/May proceed letter no later than 30 days after receipt of complete response	21 CFR 312.305(d)(2)(ii)
Breakthrough therapy designation	60 days	Grant or deny letter by day 60	FDCA Section 506, as amended by FDASIA
Fast track designation	60 days	Grant or deny letter by day 60	FDCA Section 506; as amended by FDAMA
RMAT designation	60 days	Grant or deny letter by day 60	FDCA Section 506(g), as amended by Cures Act
Qualified Infectious Disease Product (QIDP) Designation	60 days	Determine if the product is QIDP by day 60	FDCA Section 505 E; as amended by FDORA section 705
IND meeting	See R 810.04	See R 810.04	PDUFA Goals

Review Subject	Statutory Review Clock	Final Action or Response	Statutory Reference
IND Status: Sponsor's response to pre-inactivation notice	30 days	Inactivation or comment letter by day 30	21 CFR 312.45
IND Status: Sponsor's request for reactivation of IND	30 days	Reactivation or comment letter by day 30	21 CFR 312.45
IND Status: Sponsor's response to pre-termination notice	30 days	Termination or comment letter by day 30	21 CFR 312.44
PSP: Initial PSP or Amended PSP	90 days	Meet or issue written response by day 90	FDCA Section 505B(e); as amended by FDASIA section 506
PSP: Agreed initial PSP or Agreed amended PSP	30 days	Agreement or not agreement letter by day 30	FDCA Section 505B(e); as amended by FDASIA section 506
Proposed pediatric study request	120 days	Inadequate letter or written request by day 120	BPCA; FDARA implemented the 120-day review clock
Proprietary name review	180 days	Acceptability letter (including reasons if unacceptable) by day 180	PDUFA Goal; FDCA amended by FDAAA
Protocol involving exception from informed consent requirements for emergency research	30 days	Hold or proceed letter by day 30	21 CFR 50.24; 21 CFR 312.20; 21 CFR 312.30; 21 CFR 312.54

Review Subject	Statutory Review Clock	Final Action or Response	Statutory Reference
Protocol for human factor validation study for drug-device and biologic-device products	60 days	Written response by day 60	PDUFA Goals
SPA	45 days	SPA response letter by day 45	FDCA Section 505(b)(5)(B), starting with PDUFA II in 1997
User-related Risk Analysis for drug-device and biologic-device products	60 days	Written response by day 60	PDUFA Goals

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