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

**Version**: 11
**Effective Date:** January 14, 2026

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## I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide to the Center for Biologics Evaluation and Research (CBER) staff for placing a clinical study or studies submitted as part of an Investigational New Drug Application (IND) on clinical hold and for removing or maintaining the hold once a complete response is received from the sponsor.

## II. Scope

This SOPP applies to INDs for products regulated by CBER.

## 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 for an exemption to this legal requirement in order to conduct clinical studies wherein an investigational drug or biological product will be administered to humans.

**B.** Clinical studies must follow a set of laws and regulations, which are intended to protect the right, safety, and welfare of human subjects participating in clinical

studies, ensure the quality, validity, and integrity of the clinical study data, and promote the availability of new medical products to the public.

**C.** Title 21 of the Code of Federal Regulations (CFR) section 312.42 describes a clinical hold as an "*order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation*." This order can apply to one or more studies covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug or tested using the investigational biological *in vitro* diagnostic (IVD) product. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety. A study that has been placed on clinical hold may resume only after the sponsor has been notified by CBER that the clinical hold has been lifted and the study may proceed.

## IV. Definitions

**A. Clinical Hold** – An order issued by FDA to the sponsor of an IND to delay the initiation of all studies or suspend all on-going studies.

**B. Partial Clinical Hold** – A delay or suspension of only part of the clinical work requested under the IND, e.g., a specific protocol/study or part of a protocol is not allowed to proceed; however, other protocols/studies or parts of the protocol under the IND are allowed to proceed.

**C. Complete Response** – A response from the sponsor to a clinical hold which is determined by CBER to be adequate for a decision to be made on lifting or continuing the clinical hold.

**D. Incomplete Response** – A response from the sponsor to a clinical hold, which is intended to be a complete response or not identified as a complete response, yet CBER determines that it is incomplete; the response is inadequate for a decision to be made on lifting or continuing the clinical hold.

**E. Partial Response** – A response from the sponsor to a clinical hold, which is identified by the sponsor as a partial response with more data to follow.

**F. Continued hold** – A clinical hold is continued because the information provided in the submission/complete response letter does not resolve all of the deficiencies identified in the hold letter, or new deficiencies are identified in the complete response letter.

**G. Remove clinical hold** – All studies under the IND are allowed to proceed.

## V. Policy

**A.** An original IND or an expanded access treatment protocol (21 CFR 312.320) goes into effect 30 calendar days after CBER receives the IND or the protocol, respectively, unless CBER notifies the sponsor that the clinical studies described in the IND are subject to a clinical hold under 21 CFR 312.42(b). A clinical study involving an exception from informed consent under 21 CFR 50.24 must be submitted in a separated IND and is not permitted to proceed without the prior written authorization from FDA.

**B.** CBER will review all original (new) INDs within 30 days of receipt and contact the sponsor by telephone, facsimile (fax), or email (i.e., rapid communication) when a clinical hold is being imposed to briefly explain the basis for the action. If the 30-day due date falls on a weekend or holiday, CBER will contact the sponsor on the Friday before the due date or the working day before the holiday.

**C.** If FDA concludes that an issue exists that may be grounds for imposing a clinical hold, regulations require that, unless patients are exposed to immediate and serious risk, FDA will attempt to discuss and satisfactorily resolve the matter with the sponsor ***before*** issuing the clinical hold order. (21 CFR 312.42(c)). If attempts are made to contact the sponsor, e.g., via phone or email, and the sponsor cannot be contacted, the IND may be placed on hold without discussing the issues.

**1.** For original INDs, if it is determined there are issues that may be grounds for imposing a clinical hold, the review team should identify them as soon as possible to allow sufficient time for communication with the sponsor and possible resolution of the issues within 30 days of receipt of the IND.

**2.** Any discussions of the planned protocol or other aspects of the submission with the sponsor to resolve hold concerns are conducted by the review team, as appropriate to the issue being discussed, and are documented in the appropriate regulatory system and administrative file. The Branch Chief for the discipline with the hold concerns will concur with the potential hold issues before discussions with the sponsor. If hold concerns cannot be resolved with the sponsor and a clinical hold is to be imposed, the Clinical Division Director must concur with the hold decision.

**D.** CBER may place one or more studies, or parts of a study, on clinical hold when an IND is active, if it finds there are grounds for placing a clinical study or studies on hold. For these active INDs:

**1.** CBER will determine the specific context for the imposition of the clinical hold in context with what is known about the investigational drug being administered and if relevant, similar products, as well as the status and phase of the clinical study.

2. Unless patients are exposed to immediate and serious risk, CBER will attempt to discuss and satisfactorily resolve the matter with the sponsor ***before*** issuing the clinical hold order (21 CFR 312.42(c)). If attempts are made to contact the sponsor, e.g., via phone or email, and the sponsor cannot be contacted, the IND may be placed on hold without discussing the issues. The Branch Chief for the discipline with the hold concerns will concur with the potential hold issues before discussions/communication with the sponsor, which may be discussed via telephone or sent via email/fax. The Branch Chief should participate in telephone conversations with the sponsor in attempting to resolve issues prior to placing a study on hold.

3. A clinical hold on an active IND may be imposed without attempting to resolve issues when a sponsor has notified CBER that they have implemented a safety stop on a clinical study and are investigating the reasons. In this case, if it is the only issue identified and the review team and supervisors are aware and in agreement, the RPM may place the IND on hold without participation of the discipline branch chief in the teleconference/communication.

4. If hold concerns cannot be resolved with the sponsor and a clinical hold is to be imposed, the Clinical Division Director must concur with the hold decision.

    a. If potential hold issues have been communicated via telephone and cannot be resolved and the discipline branch chief has been involved in those telephone discussions, the RPM will call and place the study(ies) on hold, briefly explaining the reasons for the clinical hold.

    b. If the potential hold issues have been communicated and cannot be resolved and the discipline branch chief has not participated directly with the sponsor (for example the communications have been via email), the RPM and the discipline branch chief will call and place the study(ies) on hold, briefly explaining the hold issues.

    c. Note: if the RPM cannot contact the sponsor via telephone, the hold will be communicated either by email/fax and a follow up phone call may be scheduled as soon as possible to discuss the specific reason(s) known at the time as to why the IND is on hold. The purpose for this phone call is solely to clarify any issues that may not be clear to the sponsor; it is not intended to be a forum for refuting the hold issues.

5. Active INDs placed on hold will receive priority in issuing any letters and when attempting to resolve potential issues before placing the IND on hold (or partial hold) as well as when the sponsor has responded to the clinical hold letter.

**E.** If a clinical hold order has been imposed either on an original IND or on an active IND, the specific reasons for the clinical hold will be clearly specified and the steps the sponsor should take to address the issues, in a clinical hold letter to the

sponsor, as soon as possible and no later than 30 days after imposition of the clinical hold. (21 CFR 312.42(d)).

**F.** Grounds for imposing a clinical hold on a phase 1 study are found in 21 CFR 312.42(b)(1)).

**G.** Grounds for imposing a clinical hold on a phase 2 or 3 study are found in 21 CFR 312.42(b)(2).

**H.** If the sponsor addresses all the clinical hold issues identified in the clinical hold letter (i.e., a complete response), CBER will respond to the sponsor within 30 days of receipt of the complete response. The complete response is reviewed and a decision as to whether the study or studies may or may not proceed will be made in advance of the 30-day goal date allowing sufficient time to issue a letter to the sponsor within 30 days from receipt of the sponsor's complete response. (21 CFR 312.42(e)). For active INDs, CBER will attempt to work with the sponsor to address any remaining hold issues before the 30-day response due date.

**I.** If an amendment is submitted that provides additional information to the complete response after the 30-day review clock has started, it will be handled in accordance with the *Guidance for Industry: Submitting and Reviewing Responses to Clinical Holds*.

**J.** An incomplete or a partial response from the sponsor is not subject to the 30-day calendar response time. A sponsor will be notified that the response is not considered complete within 30 days after receipt of the response. The IND will remain on clinical hold.

**K.** A sponsor may not proceed with a clinical study on which a clinical hold has been imposed until the sponsor has been notified by CBER that the hold has been lifted (21 CFR 312.42(e)).

**L.** *SOPP 8301: Receipt and Processing of Master Files* and *SOPP 8301.1: Review and Administrative Procedures for Master Files* are to be used with this SOPP for INDs referencing to master file(s) (MF).

1. If during the review, the MF is deemed to be deficient to support a specific referencing IND, a "Master File Deficiency Letter" will be sent to the MF holder. FDA will notify the IND sponsor that the MF is insufficient to support their submission. The general subject of the deficiency may be identified to the IND sponsor, but no confidential and proprietary information in the MF will be disclosed. The details of the MF deficiency are disclosed only to the MF holder while protecting the confidential information contained in the IND. The IND sponsor and the MF holder should be advised to communicate directly with each other as soon as possible regarding how the deficiencies can be addressed.

**M.** Additional non-hold review comments may also be contained in the hold explanation letter if they are clearly designated as separate issues and are available within the 30-day timeframe so as not to delay the issuance of the hold explanation. However, as recommended in the *Guidance for Industry: Submitting and Reviewing Responses to Clinical Holds*, sponsors should submit a separate amendment to address any non-hold issues. Responses to any non-hold issue conveyed in the clinical hold letter that are submitted in the same amendment as the complete response to the clinical hold are not required to be reviewed within 30 days of receipt.

## VI. Responsibilities

**A. Regulatory Project Manager (RPM)** – Manages the review of the IND and all related submissions, ensuring review timelines are met. Schedules review team meetings and informs management of clinical hold issues and the review team's recommendation on clinical hold/no hold. Prepares clinical hold correspondence and ensures data entry into the appropriate system. Serves as primary contact with the sponsor on clinical hold decisions.

**B. Review Team –** Reviews the IND focusing on their specific discipline. Participates in review team meetings, conferring with the RPM and other review team members to determine if the IND may proceed or should be placed on clinical hold. Identifies any issues that could result in a clinical hold. Each review team member is expected to document their review, identifying the reasons for clinical hold within their review discipline, when applicable. Participates in the hold teleconference with the sponsor, when appropriate.

**C. Branch Chief –** Participates in discussions/meetings related to the hold concerns and concurs with hold issues relative to their review discipline. For active INDs, participates in teleconferences with the sponsor, along with the RPM and team members if appropriate, when trying to resolve potential hold issues and/or when studies are being placed on clinical hold.

**D. Director of the Division with review responsibilities for the clinical study or studies in the IND (Clinical Division Director)** – Makes the final decision on whether to issue a clinical hold on the IND, and for those which have received a complete response, whether the clinical hold should be lifted, modified, or remain on hold. Serves as signatory authority for letters to sponsors conveying clinical hold decisions.

## VII. Procedures

### A. For Placing a new Original IND on hold:

**1.** Review the IND (as well as solicited amendments) to determine if issues are identified that may justify imposing a clinical hold. If issues are identified, notify the RPM to schedule an internal review team meeting. **[Review Team] Note:**

Review team meetings may be face to face, via telecon, or by email discussion, as appropriate for the issue.

**2.** Schedule an internal review team meeting to determine a Hold/No Hold recommendation and identify potential hold issues. Attendees should include review team members that have identified clinical hold issue(s) and the branch chief(s) from the division(s) that have identified hold issues; other team members can be optional attendees. **[RPM]**

**3.** Participate in the internal review team meeting to discuss potential hold issues. **[Appropriate Review Team members, RPM, Branch Chief(s)]** Note: The entire review team should be aware of the potential for the imposition of a clinical hold and as relevant to the complexity of the issue, the Clinical Division Director should be made aware, e.g., cc'd on emails.

**4.** Discuss with the sponsor and attempt to satisfactorily resolve, as early as possible and practical, issues that could result in 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.** If a referenced MF has a deficiency(ies) that may result in a clinical hold being placed on the referencing IND, notify the IND sponsor that the MF is insufficient to support their submission. Identify the general subject of the deficiency(ies) without disclosing confidential and/or proprietary MF information. Details of the MF deficiency are disclosed only to the MF holder.

**i.** Refer to *SOPP 8301.1*: *Review and Administrative Procedures for Master Files* for sample recommended language informing the IND sponsor that the referenced MF is deficient.

1) Inform the IND sponsor that because of the confidential nature of FDA submissions, FDA cannot discuss the content of the referenced MF with the sponsor, but the deficiencies identified in the MF are being communicated by the FDA to the MF holder.

2) Recommend that the sponsor communicate directly with the MF holder regarding how the deficiencies can be addressed.

3) Inform the sponsor that when the MF holder has communicated to the sponsor that the deficiencies have been addressed and the MF holder's response to the deficiencies have been submitted to FDA in an amendment to their MF, the IND sponsor should respond to FDA with an IND amendment and include the signed and dated letter from the MF holder to the sponsor indicating that the MF holder has responded to FDA regarding the MF deficiency.

**ii.** Inform the MF holder as soon as possible that the MF is insufficient to support the IND. Discuss with the MF holder the deficiencies in the MF without disclosing confidential information in the referencing IND.

1) Inform the MF holder that because of the confidential nature of FDA submissions, FDA cannot discuss the content of the IND with the MF holder.

2) Recommend that the MF holder communicate directly with the IND sponsor as soon as possible regarding how the deficiencies can be addressed.

3) Inform the MF holder to submit a MF amendment to FDA that addresses the deficiencies, and to communicate with the sponsor by a signed and dated letter to the sponsor stating that the MF deficiencies have been addressed in a MF amendment to FDA.

**d.** Ensure all communications are correctly characterized and uploaded into the administrative file. **Note:** Separate review memos for the IND and MF should be prepared to ensure that confidential and proprietary information is not inadvertently disclosed to unauthorized parties.

**5.** Review responses from sponsor and finalize the hold/no-hold recommendation. **[Review Team]**

**6.** Communicate the review team's recommendation, including the rationale on clinical hold/no hold, at least two business days before the 30-day due date to the Clinical Division Director. **[RPM]**

**7.** Evaluate the review team's recommendation and decide whether a clinical hold/partial hold should be ordered. Communicate the decision to the RPM, usually via email. **[Clinical Division Director]**

**8.** Notify the sponsor of the decision to place the IND, or study or studies on clinical hold or partial hold by email, telephone, fax, or other means of rapid communication, no later than the 30-day due date, using *T820.50: Clinical Hold Rapid Communication Template*. **[RPM and Review Team, as appropriate]**.

9. Document the clinical hold notification in the regulatory system as a *Clinical Hold Notification (Hold or Partial Hold)* telecon, ensuring the correct communication code is used, and upload it into the administrative file. **[RPM]**

   **Note:** The *Clinical Hold Notification* must be entered into the regulatory system on the day the sponsor is notified. This starts the 30-day hold letter clock and changes the status of the IND from *Pending* to *Hold*.

10. Draft, route, review, sign, and issue the hold letter to the sponsor containing an explanation of the basis for the clinical hold as soon as possible, and no later than 30 calendar days after the initial hold notification to the sponsor. **[RPM, Review Team, Clinical Division Director]**

    a. For complex clinical hold issues that could benefit from an additional discussion, CBER may offer a telecon within the clinical hold letter. The purpose of the telecon is to address the sponsor's specific clarifying questions pertaining to the hold deficiencies identified in the letter. The teleconference is not intended to discuss new information, test methods, or data.

11. Enter the Clinical Hold letter into the regulatory system ensuring that the correct communication code is used, along with the reason(s) for the hold, and upload it into the administrative file. **[RPM]**

12. Ensure that the completed review memo, with supervisory concurrence, is uploaded into the administrative file. **[Review Team Members]**

**B. For Placing a Clinical Hold While an IND is in Effect/Active:**

1. Review amendments as received to determine if issues are identified that may justify imposing a clinical hold. If issues are identified use template *T843.06: Active IND Hold Review Memo* to document potential hold issues and notify the RPM to schedule an internal meeting. **[Review Team]**. Review team meetings may be face to face, via telecon or by email discussion, as appropriate for the issue.

2. Schedule and conduct an internal team meeting to discuss whether to place the IND on clinical hold. Attendees should include review team members that have identified clinical hold issue(s), Branch Chiefs from the division(s) that have identified hold issues, and Clinical Division Director. **[RPM] Note:** The entire review team should be aware of the potential for the imposition of a clinical hold.

3. Discuss whether there are any issues that may be addressed or if additional information is needed from the sponsor that could prevent the clinical hold or partial hold. **[Review Team, Branch Chief, Clinical Division Director]**

4. Discuss with the sponsor and attempt to satisfactorily resolve any potential hold issues and/or request additional information needed that could prevent a clinical hold or partial hold, **unless patients are exposed to an immediate and serious risk.** 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. Ensure the communication is correctly characterized in the regulatory system and uploaded into the administrative file. **[RPM, Discipline Branch Chief and Discipline Reviewer, if appropriate]**

    a. If a referenced MF has a deficiency(ies) that may result in a clinical hold of the referencing IND, notify the IND sponsor that the MF is insufficient to support their IND. Identify the general subject of the deficiency(ies) without disclosing confidential and/or proprietary MF information. Details of the MF deficiency are disclosed only to the MF holder.

        i. Refer to *SOPP 8301.1: Review and Administrative Procedures for Master Files* for sample recommended language informing the IND sponsor that the referenced MF is deficient.

            1) Inform the IND sponsor that because of the confidential nature of FDA submissions, FDA cannot discuss the content of the referenced MF with the sponsor, but the deficiencies identified in the MF are being communicated by the FDA to the MF holder.

            2) Recommend that the sponsor communicate directly with the MF holder regarding how the deficiencies can be addressed.

            3) Inform the sponsor that when the MF holder has communicated to the sponsor that the deficiencies have been addressed and MF's response to the deficiencies have been submitted to FDA in an amendment to their MF, the IND sponsor should respond to FDA with an IND amendment and include a signed /dated letter from the MF holder to the sponsor to indicate that. the MF holder has responded to FDA regarding the MF deficiency.

        ii. Inform the MF holder as soon as possible that MF is insufficient to support the IND. Discuss with the MF holder the deficiencies in the MF without disclosing the confidential information in the referencing IND.

            1) Inform the MF holder that because of the confidential nature of FDA submissions, FDA cannot discuss the content of the IND with the MF holder.

            2) Recommend the MF holder communicate directly with the IND sponsor as soon as possible regarding how the deficiencies can be addressed.

3) Inform the MF holder to submit a MF amendment to FDA that addresses the deficiencies, and to communicate with the sponsor by a signed/dated letter to the sponsor stating that the MF deficiencies have been addressed in a MF amendment to FDA.

**5.** Review responses from sponsor and finalize the recommendation. **[Review Team]**

**6.** Communicate the review team's hold recommendation to the Clinical Division Director using T843.06: Active IND Clinical Hold Review Memo. **[Discipline Reviewer(s), RPM]**.

**7.** Evaluate the review team's recommendation and decide whether a clinical hold/partial hold should be ordered. Communicate the decision to the RPM, usually via email. **[Clinical Division Director]**

**8.** Notify the sponsor by telephone (i.e., rapid communication) of the decision to place the study(ies) on clinical hold as soon as decision has been finalized using *T820.50: Clinical Hold Rapid Communication Template*. **[RPM, Branch Chief]**

**a.** If the sponsor cannot be contacted by telephone, the clinical hold may be communicated by email/fax. A follow up phone call solely to clarify the specific hold reason(s) may be scheduled.

**b.** If the sponsor has imposed a safety stop and it is the only issue identified and the review team and supervisors are aware and in agreement, the RPM may place the IND on hold without participation of the discipline branch chief in the teleconference/communication.

**9.** Document the clinical hold notification in the regulatory system as a *Clinical Hold Notification (Hold or Partial Hold)* telecon, ensuring that the correct communication code is used, and upload it into the administrative file. **[RPM]**

**Note:** The *Clinical Hold Notification* must be entered into the regulatory system on the day the sponsor is notified. This changes the status of the IND from *Active* to *Hold* or *Partial Hold*, as appropriate.

**10.** Draft, route, review, sign, and issue a letter to the sponsor containing an explanation of the basis for the clinical hold as soon as possible and no later than 30 calendar days after the initial hold notification to the sponsor. **[RPM, Review Team Members, Clinical Division Director]**

**11.** Characterize the Clinical Hold letter into the regulatory system, ensuring that both the correct communication code and hold reason are included and upload it into the administrative file. **[RPM]**

12. Ensure that the completed review memo (i.e., T843.06: Active IND Clinical Hold Review Memo), with supervisory concurrence, is uploaded to the administrative file. **[Review Team Members]**

**C. For review of responses to clinical holds:**

1. Review the response to clinical hold to determine whether the response is complete, incomplete, or partially complete, and update the characterization in the regulatory system. **[RPM and Review Team] Note**: Refer to Section IV for definitions.

   **a.** If the sponsor identified the response as complete, yet it is determined that the response is not complete:

      **i.** It should be characterized in the regulatory system as an incomplete response, and

      **ii.** Inform the sponsor via letter as soon as possible and no later than 30 days after receipt of the response that the 30-day clock will not start until a complete response is received. Ensure the communication is correctly characterized in the regulatory system and uploaded into the administrative file. **[RPM, Clinical Division Director]**

   **b.** If the sponsor identified the response as a partial response with more data to follow and it is determined that the response is a partial response, characterize it in the regulatory system as a partial response. **[RPM]**

   **c.** If the submission has not been identified by the sponsor as either complete or partial and it is determined that the response is not complete, characterize it in the regulatory system as an incomplete response, and inform the sponsor as soon as possible and no later than 30 days after receipt of the response that the 30-day clock will not start until a complete response is received. Ensure the communication is correctly characterized and uploaded into the administrative file. **[RPM]**

   **d.** If it is determined that the response is complete and allows for a decision to be rendered (i.e., lift or continue hold), it should be characterized in the regulatory system as a complete response. **[RPM]**

2. Initiate review of responses to the hold issues that have been determined to be complete as soon as possible in order to respond in writing not later than 30 days after CBER's receipt of the submission. **[RPM, Review Team]**

   **a.** If continue hold, partial hold, or new hold issues are identified, notify the Branch Chief, and Clinical Division Director. **[RPM, Review Team]**

      **i. Note:** For active INDs, if there are potential hold issues, the review team will attempt to discuss and satisfactorily resolve the matter with the

sponsor before issuing the clinical hold order, unless patients are exposed to immediate and serious risk.

3. Draft, review, finalize, sign and issue letter conveying partial hold, continued hold, remove hold, or a combination of these determinations within 30 days from the date of receipt of the complete response to clinical hold. **[RPM, Review Team, Clinical Division Director]**

4. Ensure the communication is correctly characterized, uploaded to the administrative file, and the correct IND status is displayed in the regulatory system. **[RPM]**

5. Ensure that the completed review memo, with supervisory concurrence, is correctly characterized in the regulatory system and uploaded into the administrative file. **[Review Team Members]**

## VIII. Appendix

Not Applicable.

## IX. References

**A.** The references below are CBER internal:

1. T 820.49: IND Deficiency Telephone Communication Template

2. T820.50: Clinical Hold Rapid Communication Template

3. T843.06: Active IND Clinical Hold Review Memo

4. 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

5. SOPP 8301.1: Review and Administrative Procedures for Master Files

**B.** The references below can be found on the Internet:

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

2. Guidance for Industry – Submitting and Reviewing Complete Responses to Clinical Holds

3. SOPP 8301: Receipt and Processing of Master Files

## X. History

| Written/ Revised | Approved By | Approval Date | Version Number | Comment |
|---|---|---|---|---|
| Xiaoqiu Tang | Sonday Kelly, MS, RAC, PMP Director, DROP/ORO | January 14, 2026 | 11 | • Procedures - removed the word "resolvable" throughout.<br>• Policy - replaced hold reasons with CFR references<br>• Policy - added information regarding Master files<br>• Added reference & steps for managing INDs referencing MFs.<br>• Removed hold notification to senior leadership.<br>• Added policy and steps for when sponsor cannot be reached for hold communications.<br>• Minor updates in procedures to clarify language regarding uploading documents into regulatory and administrative file. |
| Raza | Sonday Kelly, MS, RAC, PMP Director, DROP/ORO | February 3, 2025 | 10 | Updated policy to clarify that hold reason set forth in 21 CFR 312. .42(b)(1)(v), should be consulted with ORO. |
| Rivers/Monser/ Tang/Kelly | Sonday Kelly, MS, RAC, PMP Director, DROP/ORO | December 15, 2023 | 9 | Update to incorporate best practice for issuing IRs no later than day 21 as resources allow. Updates to process and policy. |

| Written/ Revised | Approved By | Approval Date | Version Number | Comment |
|---|---|---|---|---|
| M.Monser/ X.Tang | Sonday Kelly, MS, RAC, PMP Director, DROP/ORO | September 22, 2023 | 8 | Added policy re: imposing a hold when sponsor has stopped a study for safety reasons and is investigating. Updated procedures to include letter issuance for incomplete response to clinical hold and clinical hold memo template for active INDs. |
| M. Monser | Christopher Joneckis, PhD | June 15, 2022 | 7 | Updated to current procedures/policies. |
| M. Monser | N/A | December 11, 2020 | 6 | Technical update for retirement of EDR |
| M. Monser | N/A (reviewed by Job Aid Coordinator) | September 26, 2019 | 5 | NO CONTENT CHANGE – Technical Update to correct hyperlinks and update to current font/format |
| C. Vincent | Christopher Joneckis, PhD | May 12, 2014 | 4 | Updated to reflect legislative changes since the last revision in 1999. Added Responsibilities Section. |
| RMCC | R. Devine | April 27, 1999 | 3 | Incorporates changes resulting from comments to the Guidance to Industry - Submitting and Reviewing Complete Responses to Clinical Holds. Replaces version 2, issued 4/14/1998 |
| RMCC (Review Management Coordinating Committee) | R. Devine | April 14, 1998 | 2 | Updates the content to conform with FDA Modernization act of 1997 |
| Applications Policy Task Force | R. Devine | August 20, 1996 | 1 | First Issuance |