This information should not be considered to represent advice or guidance on behalf of the U.S. Department of Health and Human Services or any agency or office thereof.

Responding to a Clinical Hold

Refer to the **NIH SEED Regulatory Knowledge Guides** for more specific guidance on the regulation of:

- Small Molecule Therapeutics
- Biological Products

Context

A clinical hold imposed by the U.S. Food and Drug Administration (FDA) can significantly extend the duration and escalate the cost of new drug development. This is particularly challenging for emerging biotech and specialty pharma companies. This article explores the common reasons for clinical holds and offers practical advice on preventing and addressing them.

Understanding Clinical Holds

When an investigational new drug (IND) application is submitted, the FDA has a 30-day window to review it. The aim is to ensure that the study participants are not exposed to unreasonable risk and that the study is designed to meet its stated objectives. The FDA may issue a clinical hold if there are unresolved questions about critical aspects of the clinical study design, safety, non-clinical safety, or product quality of the proposed investigational treatment or if the clinical study cannot be conducted following Good Clinical Practice (GCP) guidelines and industry standards.

The FDA attempts to resolve issues with the IND applicant before imposing a hold unless there's an immediate patient risk. The Division Director responsible for the IND review typically orders the hold, which is communicated rapidly or in writing. A detailed explanation follows within 30 days. If unresolved for over a year, the IND may become inactive.

A clinical hold prevents the sponsor from administering the investigational treatment to subjects. No new subjects may receive the investigational therapy if an ongoing study is placed on a clinical hold. Typically, patients already in the study must discontinue the investigational treatment. However, in some cases, the FDA may allow ongoing administration if the potential benefits outweigh the risks of continued treatment.

Common Triggers for Clinical Holds

The guidance outlines the reasons for imposing a clinical hold on proposed or current investigations across Phase 1, Phase 2, or Phase 3 trials, as well as on protocols for expanded access and for any study that is not designed to be adequate and well-controlled.

The FDA places clinical holds based upon various concerns, including the necessity for more safety data, issues related to product quality, challenges in quantifying clinical benefits—particularly in pediatric patients at high

risk—and the rationale behind the initial dose selection and subsequent dose escalation strategy in Phase 1 first-in-human studies.

According to FDA research, product quality issues are the most common reason for placing a clinical trial on hold, followed by clinical and toxicology concerns. The manufacturing process often raises concerns for gene therapies and other next-generation therapies due to impurities, degradation products, or metabolites not qualified in a non-clinical safety model. In these cases, sponsors may need to conduct additional studies or modify their manufacturing process to lift the clinical hold.

The are several strategies for avoiding clinical holds. They include:

- Select a toxicology animal model for non-clinical safety studies that reasonably reflects the human investigational treatment accurately. Acceptability of the animal model and P/T study design can be discussed with FDA during a pre-IND meeting.
- Document and certify the manufacturing process to avoid introducing anticipated risks like impurities. Acceptability of the in-process, batch, and final product testing plans can be discussed with FDA during a pre-IND meeting.
- Incorporate sensible safety projections in the Informed Consent Form (ICF).
- Engage experts to support all required disciplines (manufacturing, non-clinical, and clinical) when preparing a robust IND application and clinical development plan.
- Emphasize the articulation of information, using medical writers to weave data into a narrative that clearly communicates your intended development activities to FDA reviewers.

Addressing a Clinical Hold - Key Questions

If a clinical hold is imposed, sponsors should proactively communicate with the FDA to answer the following questions:

- **Is the FDA imposing a full or partial clinical hold?** With a partial hold, some trial investigations can continue. It's crucial to clarify whether dosing can continue without interruption in already-enrolled patients to prevent disruptions in data collection.

- **What is the FDA's concern?** It's essential to understand the nature of the concern and the detailed reasons behind the clinical hold to plan an appropriate resolution strategy.

- **Who should be notified?** Sponsors must develop a communication strategy to inform ethics committees, institutional review boards, partners, sites, participants, and other entities that might be contractually required to be notified about a clinical hold.

Sponsors should exercise due diligence in supporting an IND. Engaging experienced regulatory consultants can provide the necessary oversight to help identify the full range of risks, from those that may exist for patients to those that can impact corporate reputation.

Effective Management of Clinical Holds

Managing clinical holds is crucial for life sciences companies. The utmost priority is the safety of clinical trial participants, and all actions should reflect this commitment. Here are the key steps for initial FDA communication and subsequent actions:

- Determine Hold Type – Quickly ascertain whether the clinical hold is full or partial. A partial hold may allow some trial activities, like dosing enrolled patients, to continue while stopping new enrollments.
- Identify Concerns
    - CMC or Clinical Issues – Clinical holds can arise from chemistry, manufacturing, and controls (CMC) issues or clinical problems such as unexpected serious adverse events. Identifying the exact cause is essential for crafting an effective resolution strategy.
    - FDA's Specific Concerns - The FDA will provide a full list of reasons for imposing a clinical hold within 30 days. Use the initial communication to gather as much information as possible to inform your strategy and communication.
- Develop a Communication Strategy – Establish a communication plan to inform clinical site investigators, co-development partners, and other relevant parties. Public companies should also consider investor disclosure obligations.
- Material Information – Treat the clinical hold as material non-public information under federal securities laws. Decide if it's necessary to restrict trading or disclose the hold in ongoing offerings or corporate transactions.
- Develop a Resolution Strategy – Create a comprehensive strategy to address the FDA's concerns. This may involve additional studies, manufacturing process modifications, or study design revisions.
- Communicate with the FDA – Maintain open and proactive communication with the FDA. Address the FDA's concerns in writing and discuss your proposed resolution strategy with your lead reviewer.
- Implement Changes - After developing and communicating a resolution strategy to the FDA, implement the necessary changes. This could include protocol adjustments, training improvements, or enhanced safety measures.
- Request Lift of Hold – Once all FDA's concerns are addressed, request the hold be lifted. The FDA will review the changes and determine if the clinical trial can proceed.
- Ensure Ongoing Compliance – After the hold is lifted, comply with all regulatory requirements to prevent future holds. This includes regular monitoring and reporting to the FDA.

These steps are designed to navigate clinical holds effectively, ensuring participant safety and regulatory adherence.

Conclusion

Proactive preparation and a detailed understanding of the regulatory requirements can mitigate the impact of a clinical hold. Companies can navigate clinical holds more successfully by maintaining high standards in study design, documentation, manufacturing, and preparing for effective communication with the FDA. Preparation and proactive communication are crucial to effectively navigating clinical holds and minimizing trial disruptions.

Resources

- IND Application Procedures: Clinical Hold
- Submitting and Reviewing Complete Responses to Clinical Holds (Revised)
- Guidance for Industry and Clinical Investigators – The Use of Clinical Holds Following Clinical Investigator Misconduct