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Bridging Discovery and Delivery: The Essential Role of INDs in Biopharmaceutical Development

A Guide to Understanding the IND Filing Process

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Federal law dictates that a drug must have an approved marketing application before it can be transported across state lines (i.e., placed into interstate commerce). New drug developers almost always must deliver investigational drugs to clinical investigators across the country to conduct the studies required to obtain marketing approval, so they are compelled to request an exemption from this federal law. The Investigational New Drug (IND) application is the mechanism through which sponsors acquire that exemption from the FDA,[1] which processes approximately 1,500 such applications every year.[2]

The FDA's core objectives during the IND review process are primarily twofold: to safeguard the rights and well-being of the study subjects and, particularly in Phase II and Phase III clinical trials, ensure that the design and conduct of clinical trials are sufficient for a comprehensive evaluation of a drug's safety and efficacy.[3]

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IND Categories

INDs primarily fall into two distinct classifications: Commercial and Research.

A **Commercial IND** is generally pursued by a corporate entity that intends to bring the product to market through a marketing application. A **Research IND** is often sought by an individual investigator, academic institution, or nonprofit organization with no commercial intentions. Their investigations are exclusively conducted for research purposes, have shorter durations, and may yield research findings intended for publication in peer-reviewed journals.

Several other distinct subclasses of INDs exist,[5] including **Investigator INDs**, which encompasses submissions by physicians who both initiate and oversee investigations. They are directly responsible for the administration or dispensation of the investigational drug and may later opt for a research IND to propose the study of an unapproved drug or even an approved product for novel indications for previously unexplored patient populations.

Emergency Use INDs permit the use of experimental drugs in emergency situations where there is insufficient time for a more formal IND submission. Emergency Use INDs may also be utilized with patients who don't meet the criteria of an existing study protocol or when an approved study protocol is not available.

Treatment INDs are submitted for experimental drugs that have shown promise in clinical testing, especially for severe or immediately life-threatening conditions. They are typically issued while final clinical trials are in progress, and FDA reviews are underway.

Exploratory INDs are submitted to conduct limited exposure studies prior to initiating traditional Phase 1 safety and tolerability studies. These studies can be useful to establish nonclinical and clinical strategies, as well as provide insights into chemistry, manufacturing, and controls. They can play a pivotal role selecting candidate drugs to advance and in planning future human studies.[6]

What Does the FDA Seek in an Initial IND Submission?

An IND application includes information in three main areas:

01

Animal Pharmacology and Toxicology Studies:

A summary of animal studies conducted to assess the safety of the drug for administration to humans, as well as studies designed to assess the drugs mechanism of action and potential efficacy in the intended indication.

02

Manufacturing Information:

This covers the characterization stability and, controls of the drug substance production, as well as the composition, stability, and controls of and drug product production to ensure consistent batch quality

03

Clinical Information:

A description of any previous human experience with the drug, a comprehensive protocol for the initial trial to be conducted under the IND including plans for safety monitoring, the qualifications of overseeing clinical investigators, and commitments to obtaining informed consent, undergoing institutional review board scrutiny, and adhering to IND regulations.[7]

There are a few common pitfalls that can impede a successful IND application.[8] Fortunately, they are easily actionable, and therefore easily preventable.

IND applications can have incomplete nonclinical data, including insufficient safety, pharmacodynamic, and/or pharmacokinetic information. This can be avoided by ensuring that the package of nonclinical studies submitted in the application adhere to applicable ICH and FDA guidelines including use of appropriate animal models, meticulously designed assays, and thorough toxicology evaluations.

Another shortcoming can be a lack of detailed information around manufacturing processes, control measures, and product characterization. The application should include an exhaustive description of manufacturing processes that highlight critical steps, quality control protocols, and data demonstrating batch consistency.

Weak trial design can be another issue, especially when it involves inadequate monitoring of safety and protection of human subjects. Other issues can include inadequate sample sizes, vague clinical endpoints, or poorly defined control groups, which can trigger regulatory concerns. Robust effort should be invested in crafting well-designed trials, with clearly delineated endpoints and the implementation of rigorous statistical analysis plans. Involving more stakeholders in this process can strengthen the application.

Lastly, inadequate regulatory documentation can derail the process. Incomplete or poorly prepared investigator brochures, informed consent forms, and safety reporting procedures can lead to delays. Paying meticulous attention to compiling comprehensive and accurate regulatory documentation that aligns with existing guidelines and ensures consistency across all submission components is crucial.

Pre-IND Meetings

Pre-IND meetings provide substantial value in shaping a drug development program, especially when sponsors have unanswered questions beyond the scope of FDA-provided guidelines and information. These early interactions with FDA staff can provide proactive measures that prevent potential issues. Pre-IND meetings can give sponsors essential insights into the preparation of a comprehensive IND application. Utilizing FDA resources streamlines the process and benefits established entities and smaller organizations less acquainted with FDA interactions, alike.

The benefits of pre-IND meetings include reducing time to market by identifying and sidestepping unnecessary studies and ensuring that relevant ones are designed to yield meaningful data. These encounters also drive FDA support for proposed strategies, minimize the risk of clinical holds, foster creativity, provide regulatory insights, and define program endpoints and objectives. In short, pre-IND meetings can be a crucial mechanism for sponsors to proactively engage with the FDA, ensuring a smooth drug development journey, efficient use of resources, and the formulation of a well-defined strategy.

Real World Example

A small United Kingdom-based pharmaceutical company sought assistance with the IND activities for a novel compound for asthma. To facilitate the product's US development, a team of consultants was assembled comprising regulatory, clinical, nonclinical, and chemistry, manufacturing, and controls experts. This team provided vital strategic input and guidance for appropriate development.

During the pre-IND phase, the collaboration facilitated a pre-IND meeting with the FDA, crafted the client's pre-IND briefing document, conducted rehearsal sessions, represented the client as the regulatory representative, reconciled discrepancies, and clarified issues, all to the client's satisfaction.

Following the successful pre-IND meeting, the team prepared and submitted the client's IND application, which was accepted by the FDA. Queries around nonclinical findings were answered through the development of response strategies, resulting in the IND application's subsequent clearance within 30 days.

Afterwards, the team assumed full responsibility for IND maintenance throughout all subsequent activities and served as the client representative for all FDA interactions. The collaboration established trust and reliance from the client, resulting in a comprehensive and successful IND application that foresaw and navigated essential obstacles and brought a new product to market.

Partner for Success

Drug developers have many compelling reasons to enlist the services of a consulting firm, and Syner-G, specifically, when preparing an IND submission. The experts at Syner-G have a deep well of experience in every stage and aspect of the IND process; a crucial characteristic when no two clients, products, or projects are alike.

Chemistry, manufacturing, and control and regulatory requirements for new products vary widely based on any number of factors, including the complexity of the molecule, formulation, indication, patient population, and more. Syner-G's value proposition lies in the ability to assemble a team of experts, each skilled and practiced in the minutia of their specialty. What's more, the value of staying up to date on the many, many moving parts that comprise the exploratory, development, regulatory, and approval stages of drug development cannot be overstated.

Of course, the customer can define the scope of any project. However, true security lies in knowing that while the consulting partner will bring a thorough and precise focus on the stated project parameters, that same partner is fully capable of developing and managing the product's path even further, if required.

Partnership with the right consulting firm is just that – a partnership between two entities that rely on the ingenuity, talents, and experience of the other to navigate a constantly changing healthcare landscape and bring new, lifesaving therapies to patients.

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