Worldwide Clinical Trials

From Concept to Market: The Strategic Role of An IND in Drug Development

Moving Beyond “May Proceed”

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Abstract

An investigational new drug (IND) application is a necessary milestone for drug developers looking to conduct any trials in the U.S., including first-in-human (FIH) and later-phase programs completed in other regulatory jurisdictions. While several regulatory pathways are available internationally, the IND, overseen by the FDA in the U.S., is particularly notable for its thorough and product-specific approach. A pre-IND (PIND) and IND application process thus serves as an optimal vehicle for business planning purposes and communicating with various external stakeholders who ultimately dictate investment decisions and market access. This white paper highlights the benefits of opening an IND beyond the initial enabling regulatory requirements, with a focus on strategic business opportunities through collaboration and networking, enhanced opportunity for government and private investments, and emphasizing the benefits that can accrue when using the IND process to frame clinical development and marketing considerations which may occur globally.

A Successful IND — As a First Step in a Product Narrative

Drug developers have multiple routes to gain regulatory approval for FIH trials or other later-phase development opportunities outside the U.S. These include clinical trial authorizations (CTAs) as primary options in other regulatory jurisdictions. The U.S. requires an IND before human exposure to an investigational drug, and these applications fall under the U.S. FDA's jurisdiction.[1]

Outside of the U.S., each country has unique requirements and processes for authorizing an investigational drug. For example, E.U. and Canadian agencies require a CTA submission. Whereas an IND submission is product-specific, a CTA submission in another region is protocol-specific. Those who review the data in the application process include a range of subject matter experts and will examine the rationale and enable nonclinical information to inform the details of proposed trial designs, providing a preliminary template for strategic clinical program development.

> With an IND, the sponsor can effectively begin framing a development journey for an entire program, creating a product narrative from the onset of clinical research.

Scheduling the Meeting	Preparation	FDA Review	The Meeting	Follow-Up
Sponsor submits requests including, briefing package that outlines proposed development plan, key nonclinical and clinical questions, and specific areas where feedback is sought.	Briefing package covers drug's background, proposed indication, CMC, nonclinical and clinical data, ~10 questions per guidance for FDA to address during meeting.	FDA reviews briefing package and prepares responses to sponsor's questions to either confirm data adequacy or identify potential issues or gaps requiring remediation.	Sponsor and FDA review technical and scientific information which will enable a proposed clinical program. Sponsor and FDA interaction may occur either through written responses only (WRO), teleconference, or in-person meeting.	After meeting, FDA provides written summary that sponsor uses to refine the proposed study and/or program to facilitate IND application.

***Figure 1**. The PIND (Type B) to IND transition.[2,3]*

Phase I programs, in particular, provide an empirical examination of product attributes in humans, which have been suggested based on nonclinical data or earlier phase pilot clinical programs that may have been conducted outside of an IND. Questions include those related to confirmation of manufacturing procedures, absorption distribution, metabolism, and elimination, as well as confirmation of acceptable safety margins based upon exposure levels in Good Laboratory Practice (GLP) toxicology programs. In some cases, clinical trial designs additionally provide preliminary evidence of target engagement, suggesting ultimate clinical utility. With the acquisition of an IND, a sponsor will also have access to an assigned regulatory project manager for continuity throughout the development journey — an invaluable resource given the emerging opportunities and challenges inherent within product development.

A Successful IND — As a Pathway for Continual Engagement

Frequent interactions with regulatory agencies, especially in the early stages of drug development, can significantly influence program development's extent and detail. These protocol and program-related design discussions may also impact eventual policy decisions regarding formulary placement and reimbursement, thus affecting market penetration and commercial success. The drug's targeted indication and the administrative flexibility shown by various reviewing divisions of the FDA are consistent with ICH conventions and play a crucial role in determining the optimal method and style of regulatory engagement.[4]

For example, the Office of Oncologic Diseases within the FDA provides scientific, clinical, and regulatory oversight during the development and approval of drug and biologic treatments for cancer and hematologic malignancies. Oncology IND applications often adopt an urgent, patient-centric tone due to the critical nature of cancer treatments in a population characterized by significant morbidity and mortality. These applications may emphasize the immediate need for new therapies and the potential to save lives, which can resonate strongly with regulators. Primary pharmacology, a relationship between exposure and pharmacodynamics, and potential clinical effects, particularly during a PIND interaction, are notable points of emphasis. The extent and breadth of innovative programs and projects within this division offer a panoply of diverse development options that the process of an IND application can catalyze.[5]

However, the FDA is not a monolithic structure, and different therapeutic areas may emphasize selected aspects of program design. For example, applications within the division of neurology or psychiatry may focus on long-term outcomes or adopt a conservative stance at the time of an IND application, particularly regarding safety pharmacology or GLP toxicology observations. Indeed, a more conservative stance is appropriate in many neurological or psychiatric indications because the pathophysiologic foundation for each indication and, therein, the potential efficacy and safety of new treatments rests upon biological processes that are often less well understood. Extensive, convergent, multidisciplinary efforts are required to provide validation of the potential clinical rationale of any new therapeutic entity. Additionally, the often subjective and operator-dependent nature of assessments within this therapeutic area frequently prompts exquisite attention to elements of trial design and analyses and investigative staff accreditation, training, and surveillance mechanisms to assure assay sensitivity.

> During the IND application process, the value of a new therapy to multiple stakeholders can be highlighted, framing opportunities and risks associated with clinical development.

Sponsors can propose and elicit comments on a number of different options for protocol and strategic program design at the time of an IND application through discussions with experts in the FDA. By highlighting the potential for significant, lasting improvements in how a patient "survives, feels, and functions" during the IND application process, developers can communicate the potential value of therapies to multiple stakeholders and better characterize the risk attended with clinical development given the attrition frequently noted for new chemical or biological entities across therapeutic areas.[6,7]

A Successful IND — As a Vehicle for "Regulatory Crosstalk"

If a developer plans to market a drug in the U.S., even if the supporting trial data is derived from studies conducted internationally, registering studies under an IND is vital. This approach allows the sponsor to engage with the FDA early, even before starting clinical trials, or to position clinical trial data obtained under other regulatory jurisdictions for critical review. The scientific and technical exchange facilitates an appreciation of possible enhanced or restricted text regarding product labeling. The IND pathway thus enables the sponsor to incorporate the technical, scientific, and clinical insights gained from PIND meetings and other regulatory engagements, such as INTERACT and Type C and D meetings under the Prescription Drug User Fee Act (PDUFA VII), into a comprehensive development program. This preparation helps anticipate the scrutiny expected during dossier reviews for subsequent studies.

A successful IND application permits informed "crosstalk" across regulatory agencies.

For sponsors that intend to market a drug in the U.S. and the E.U., these early meetings with the FDA can also set expectations for the next steps. This may include the need for a Parallel Scientific Advice meeting where regulators from both the FDA and the EMA jointly provide feedback on the drug's development from both agencies' perspectives.[8] While other regions also have appeal, including applying for a clinical trial notification (CTN) in Australia, careful consideration for the benefits and potential limitations as they may impact the overall program will inform the best development pathway for a given therapeutic intervention by balancing perceived benefits against the recognized limitations.

As an example, aligning with international standards via an IND submission also enhances the credibility of nonclinical as well as clinical trial data they may have supported the application, facilitating regulatory submissions to other global health authorities, including the EMA and Asia-Pacific agencies. Strategically, IND authorization signifies regulatory validation of the investigational drug's safety profile, plausible nonclinical or limited clinical data suggesting therapeutic utility, and an overall development plan, enhancing investor confidence and attracting potential partners or collaborators. With IND status, pharmaceutical companies can pursue licensing agreements, co-development partnerships, or funding opportunities with industry peers, academic institutions, or government agencies.[9] By deliberately managing IND applications, companies can mitigate risks and enhance the efficiency of the drug development process.

Products that potentially treat serious or life-threatening conditions and demonstrate the potential to address unmet clinical needs based upon nonclinical data or clinical information additionally may receive expedited development and review through more frequent FDA meetings, a rolling review of an eventual New Drug Application (NDA) or Biologic License Applications (BLA). For example, these products may qualify for accelerated approval based on a definable surrogate endpoint as a candidate and a priority review mechanism that reduces standard review time by approximately ten months. Innovative regulatory-sanctioned programs help streamline the development process, accelerating the path to clinical trials and bringing new drugs to market more quickly.[10,11]

Marketing applications submitted to the FDA between 2008 and 2012 that utilized a PIND meeting had a median clinical development time (CDT) of 6.4 years; the applications with no PIND meeting had a median CDT of 8.3 years.[12]

Marketing applications submitted to the FDA utilizing a PIND have historically resulted in shorter clinical development times.

Successful IND — As a Strategic Business Opportunity

Securing FDA approval through an IND application boosts a product's credibility and provides attestation to scientific and technical staff capabilities associated with drug discovery and translational clinical research capability. As validation, a fully unencumbered IND also attests to an organization's business acumen and management, given the multiple hurdles and milestones that management must successfully navigate in the process. By opening an IND, a developer showcases a well-thought-out development plan that covers the integration of various disciplines, meeting all regulatory requirements for a given stage of development, with business acumen that has facilitated the successful management of corporate resources.

> Collaborative partnerships and alliances increasingly characterize the pharmaceutical industry, and a successful IND application catalyzes this handshake.

Various strategic advantages may also occur following successful IND application, including financial opportunities (e.g., additional fundraising or partnerships), potential marketing positioning, intellectual property development, and risk mitigation, as sponsors continue to gather data after the IND that informs future discovery and development research within the discovery pipeline.

The Strategic Advantages of an IND

Strategic Framework	Strategic at program level	Brisk, predictable clearance (30 days)	A first step in creating a product "narrative"	A testament to R&D management (peer-reviewed)
Operational Benefits	Intellectual property development in the U.S.	Collaborative partnerships & alliances	Risk mitigation strategies through data sharing	Streamlined FDA process across phases
Optimal Outcomes	Access to innovative programs through the FDA	Enhanced visibility & regulatory crosstalk	Catalyst for demonstrating value in large markets	Moving beyond "may proceed"

***Figure 2**. The IND carries significant strategic advantages across all components of development, ultimately leading to optimal outcomes.*

Complex interrelationships between biotechnology, large pharmaceutical companies, academia, emerging biotechnology, and small pharmaceutical companies are increasingly the norm.[13] The acquisition of an IND permits a sponsor to position an asset attractively, emphasizing commitments to innovation and prompting the possibility for shared resources and knowledge exchange, which would provide valuable insights for product development (Figure 2). Indeed, a successful IND acquisition can increase stock valuations for publicly traded companies.[14]

A Successful IND — As a Catalyst to Define Value

The industry has a well-known saying: regulatory agencies dictate approval, physicians dictate adoption, but payers ultimately control access. Amongst diverse mechanisms commonly employed as gating mechanisms by commercial insurance plans include specialty-based prescribing, prior authorizations, and step edit programs in which other agents also approved for the same indications must demonstrate a failure to remediate signs or symptoms before authorization for a new therapeutic

entity will occur. In some circumstances, even with authorization, there are quantity limits and, on occasion, a need to demonstrate improved clinical outcomes for reauthorization. The FDA's feedback on program design, accessible through an IND process, can be crucial to the payer and provider community, even though it may occur long before achieving market authorization. Indeed, program initiatives to demonstrate a new therapeutic entity's "value proposition" are often catalyzed by a successful IND application, creating a parallel workstream gathering data that would appeal to many different stakeholders.

When a developer's efforts show promise and have the FDA's sanction based upon available data, demonstrated through well-documented regulatory exchanges, payers and providers are more likely to recommend and reimburse a new drug when it reaches the U.S. market as there is an inherent validation process that provides attestation to data integrity and potential clinical meaningfulness. Finally, as the U.S. boasts one of the largest healthcare markets, an IND facilitates early access to a large patient base through studies conducted under this umbrella, acknowledging regional differences that may occur within standards of care. With high per capita healthcare costs, surveyed payers indicate that clinical trial data on safety and efficacy is crucial to their review process, focusing on the drug's safety profile and its potential impact on costs associated with healthcare utilization.[15,16] This process begins with initiating an IND as part of a strategic and transactional program.

A Successful IND — As an Inflection Point Beyond "May Proceed"

At the conclusion of a successful IND application, sponsors will, in optimal circumstances, receive a "may proceed" designation from the agency. Yet the drug development landscape constantly evolves, with emerging trends impacting various trial design elements and eventual commercialization. These range from the emergence of personalized medicine initiatives[17] to digital health technologies that facilitate study assessments in many different environments, highlighting the need for integrated R&D teams evaluating advanced technologies in nuanced patient populations.[18,19] In a dynamic and changing regulatory environment, the benefits of a comprehensive review of nonclinical and clinical data by subject matter experts within the FDA provide a significant inflection point for the development of therapeutics through a PIND and IND application process.

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