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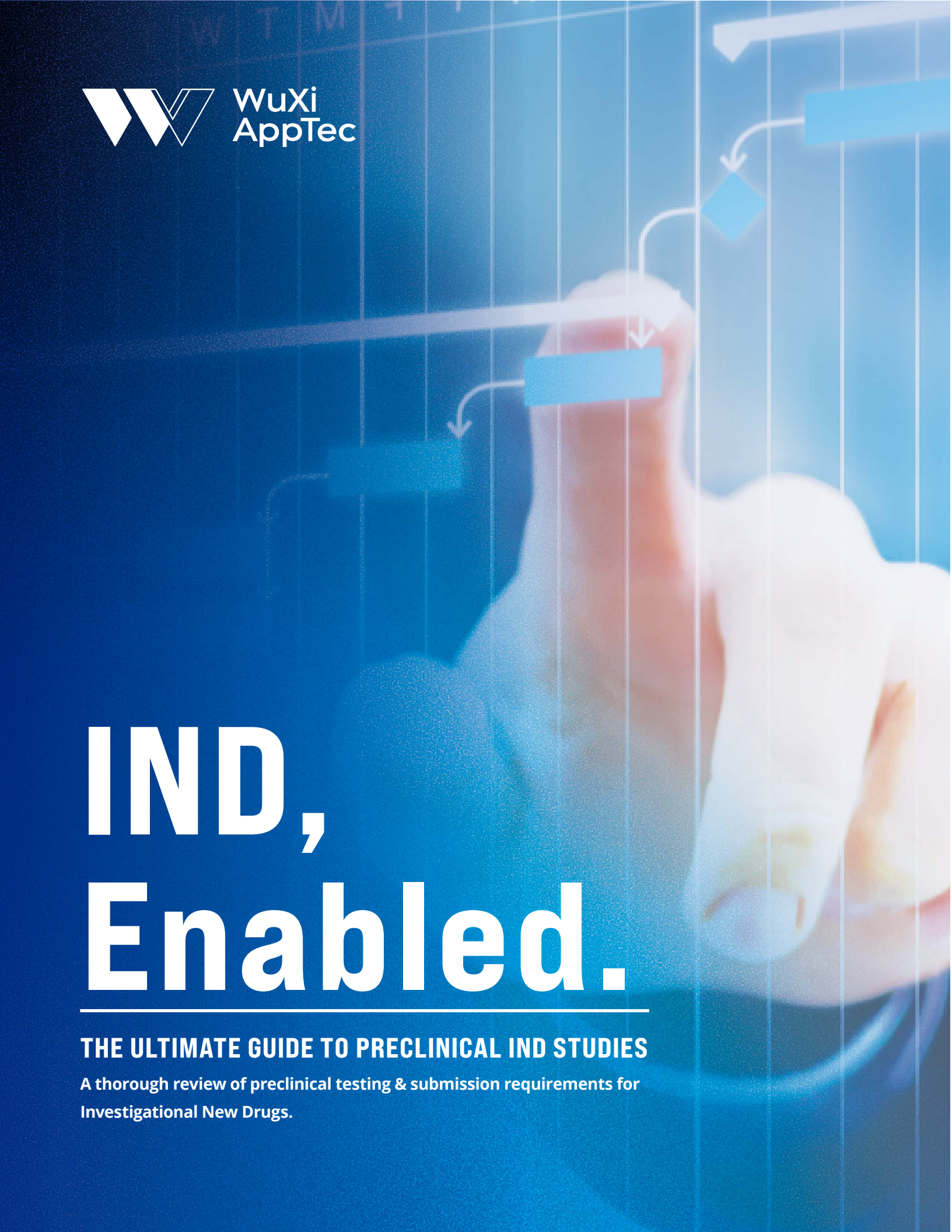

IND, Enabled.

THE ULTIMATE GUIDE TO PRECLINICAL IND STUDIES

A thorough review of preclinical testing & submission requirements for Investigational New Drugs.

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CHAPTER 1

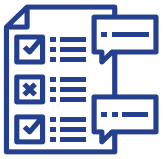
INTRODUCTION TO IND STUDIES

IND-enabling testing is a cornerstone of the drug development process, helping researchers predict safety concerns and estimate safe and efficacious starting doses for clinical trials.

To that end, an Investigational New Drug (IND) application is the first regulatory step drug developers must take when preparing an investigational drug for human clinical studies. According to the Food and Drug Administration (FDA), IND applications must include:

Animal Pharmacology and Toxicology Studies

Manufacturing Information



Clinical Protocols and Investigator Information

WHAT IS IND-ENABLING TESTING?

During a new drug's early preclinical development, sponsors have to demonstrate that a compound is reasonably safe for initial use in humans and exhibits pharmacological activity that justifies commercial development.

Data gathered in a series of IND-enabling tests to establish preclinical safety are required to begin first-in-human (FIH)/Phase 1 studies.

IND-enabling testing routinely includes a series of toxicology studies in two species with supporting pharmacokinetic and bioanalytical data, safety pharmacology studies, and genetic toxicology. However, a comprehensive IND-enabling program is dependent on the full clinical plan: class of drug, route of administration, dose, duration of treatment, and planned indication.

IND & THE DEVELOPMENT CYCLE

IND-enabling studies provide essential data and information to support the submission of an IND application to regulatory agencies. The drug development cycle typically consists of several phases, and the IND-enabling studies represent a critical step before moving into clinical trials. Here's how IND-enabling studies contribute to the drug development process.

01

Early Development & Discovery

Before IND-enabling studies, drug discovery and early development involve identifying potential drug candidates through laboratory research and preclinical testing. Promising compounds are selected for further development based on their potential therapeutic effects and safety profiles.

02

Preclinical Development

IND-enabling studies bridge the gap between early discovery and clinical trials. These studies involve comprehensive pharmacological and toxicological assessments of the drug candidate in laboratory animals to gather crucial data on safety, efficacy, and potential risks.

03

Objective of IND-Enabling Studies

The primary goal of these studies is to generate sufficient data to support the safety and feasibility of testing the drug candidate in humans during clinical trials. IND-enabling studies help researchers and regulatory agencies assess the potential risks and benefits of the drug candidate.

04

Regulatory Submission

Once IND-enabling studies are complete, researchers compile the data and submit an IND application to regulatory agencies (e.g., the U.S. Food and Drug Administration, FDA). The IND application includes comprehensive information on the drug candidate, study protocols, preclinical data, and plans for clinical trials.

05

Regulatory Review

Regulatory agencies review the IND application to ensure that the preclinical data support the proposed clinical trial and that the clinical trials will be safe and ethically conducted. The review assesses the quality, safety, and efficacy data from preclinical studies and ensures that ethical standards are met.

06

Clinical Trials

If the IND application is approved, the drug candidate can advance to Phase I. Phase II and III clinical trials have additional preclinical study requirements, including longer duration studies and some specialty toxicology studies depending on the patient population and indication. Phase II and III trials will continue testing the drug in human subjects to further evaluate safety, dosage, efficacy, and side effects.

07

Post-Approval Activities

Successful completion of clinical trials may lead to a New Drug Application (NDA) submission for regulatory approval. **Post-approval activities include ongoing safety monitoring, additional studies, and market launch.**

IND-enabling studies serve as a critical link between early development and discovery and human clinical trials. They provide the necessary data to support regulatory approval for testing a drug candidate in humans, ensuring that the potential benefits outweigh the risks. The successful completion of these studies is a pivotal milestone in the drug development process, influencing the progression of a potential therapeutic from the laboratory to patients.

WHAT DOES IND TESTING INCLUDE?

Generally, there are four main categories that IND-enabling studies fall under.

Drug Metabolism & Pharmacokinetics (DMPK)

DMPK studies play an important role in providing a thorough examination of the absorption, distribution, metabolism, and excretion (ADME) properties of an experimental drug. Obtaining this information in the preclinical stage helps researchers guide chemical structure optimization and predict *in vivo* PK properties and drug-drug interaction (DDI) potential in humans.

DMPK studies start *in vitro* with:

- Physicochemical properties analysis
- Permeability assays
- Solution-phase stability assays
- Protein binding and partitioning assays
- Drug-drug interaction (DDI) assays
- Metabolic stability

From there, researchers move on to *in vivo* studies. These are typically performed in animals, whose pharmacokinetics are most similar to humans, as they will be the most translatable models available to support the transition into human clinical trials. These studies may include:

- Non-radiolabeled or radiolabeled mass balance studies
- Pharmacokinetics
- Quantitative whole body autoradiography (QWBA) studies
- Metabolite identification

Toxicology

Preclinical toxicology assessments are critical to the progression of a new drug candidate. Like IND-enabling testing as a whole, the safety assessment program strategy will differ for small molecule and biologic therapies.

For example, small-molecule nonclinical safety programs require general toxicology studies in two species (rodent and non-rodent) as well as mutagenicity and cytogenetic studies to determine genotoxicity. Small molecules can form one or more metabolites *in vivo*, which could be relevant to human risk.

Biologics, on the other hand, may require studies in only one species, based on availability of pharmacologically relevant animal models. Also, these molecules are not considered to interact with DNA within cells, so genotoxicity studies are not required. Unlike small molecules, these therapies do not form metabolites, but are degraded into peptides or amino acids and/or excreted.

Safety pharmacology

Safety pharmacology tests to determine the effect of the drug on critical organ systems in the body, including cardiovascular, pulmonary, and CNS. Additional systems can be evaluated if a drug is expected to have effects on GI motility, renal function, etc. For small molecules, these are often stand-alone studies; for biologics, these parameters can often be included in the toxicology study designs.

Toxicology studies should include single-dose and repeated-dose tests. To enable initial human trials, additional studies like immunotoxicity and local tolerance studies may also be required.

Following initial studies in humans, additional safety testing will be required for the drug to progress through clinical trials. These include:

- Reproductive and development toxicity
- Carcinogenicity

Bioanalysis

Preclinical bioanalysis flows through the entire IND-enabling testing process. This involves identifying and quantifying drugs and metabolites in various biological matrices, such as blood and plasma. The FDA released guidance for the industry on bioanalytical method validation to help drug developers ensure the bioanalytical quality of their data.

Based on validated methods, researchers need to conduct tissue sample analysis and collect data through studies including:

- Pharmacokinetic and/or toxicokinetics
- Immunogenicity
- Biomarker assessment

Developing these validated methods according to the FDA's guidance is an in-depth process in and of itself. Later, we'll explore how and where developers can find support.

CHAPTER 2

UNDERSTANDING REGULATORY NEEDS

The development path for bringing new drugs and therapeutics to market requires extensive planning to meet the short- and long-term needs of products intended for global registration.

Because international regulatory agencies may have different requirements for IND submissions, it might seem more straightforward to file separately; however, planning a comprehensive global IND submission has the potential to save drug developers time and money.

THE IMPORTANCE OF A GLOBAL PROGRAM

A global IND program reduces the possibility of conducting duplicate studies, and because it is a unified program, it enables faster expansion into foreign markets. Still, team members may not understand the different requirements of each approval pathway.

To achieve optimal results, developers must make the decision to file a global IND submission early in the planning phase. With appropriate foresight, they can ensure all studies adhere to current standards, typically including the U.S. Food and Drug Administration (FDA), Organization for Economic Co-operation and Development (OECD), European Medicines Agency (EMA), and the National Medical Products Administration (NMPA) of China.

Drug development teams pursuing global IND submissions can categorize these significant regulatory differences into three areas:

- Study conduct (including personnel roles, documentation, and changes in the scope of work)
- Reporting expectations
- Archiving procedures

BUT IF DEVELOPERS KNOW WHAT TO LOOK FOR, SUCH CHALLENGES AND DELAYS CAN BE MINIMIZED.

Detailing the Study Protocols & Study Conduct Elements

Many study designs are essentially the same, but the fundamental terminology, documentation requirements, and explicit participant roles and responsibilities can differ.

Both the NMPA and OECD require unique identification for each study, and test systems need to be traceable to their origin. However, U.S. FDA regulations and Good Laboratory Practices (GLP) requirements state that they only need to be adequately labeled with specific information. These minor details may feel like a matter of semantics, but noting these nuances can help ensure a submission meets all the requirements and does not result in potentially significant deviations.

Identification of the testing facility, Testing Facility Management (TFM), study director, principal investigators, and contributing scientists is critical to all regulatory bodies. That said, some differ in the level of authority, ability to allocate resources, and required signatures on final documents (like study protocols and protocol amendments).

While the single point of control for each study is the study director, the overall authority of TFM is broader and defined in the OECD and EU regulations.

STUDY DESIGN

Study designs also vary between regulatory agencies, though the U.S. FDA and OECD are more similar due to the adoption of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

One example of study design variation is that the NMPA requires a laboratory to conduct certain studies within a double barrier system, while the U.S. FDA follows conventional housing guidelines. Differences also arise where the NMPA requires acute studies to adhere to GLP, which is unnecessary when filing under the U.S. FDA.

Differing Requirements

The test system requirements for *in vitro* and *in vivo* studies are examples of expectations that differ between regulatory bodies. Some details like identifying test, control, and reference articles vary slightly, although all have the same essential meaning; some are more explicit depending on the agency.

Lastly, the U.S. FDA also stipulates that clinical pathology and gross pathology findings be available to the pathologist during the histology exam, yet neither the NMPA nor the OECD specifically states this requirement. There are other instances where the study protocol's cohesiveness and clarity are directly affected by the countr(ies) intended for IND submission, so it's essential to understand what elements are shared and those that differ when designing studies.

Reviewing Reporting Expectations

Reporting standards vary among regulatory agencies, and the scope, content, and context of IND submissions can differ even in the smallest of details. To stay attuned to these specifics, drug developers must diligently review the comprehensive guidelines each regulating agency follows and stay abreast of regulatory changes and ongoing initiatives that change from time to time.

Other notable differences for report finalization are that the NMPA and OECD require a signature by the testing facility management and a unique identification number for the NMPA. And even though the OECD does not require an amendment if reformatting for submission, one may need to be provided to meet U.S. FDA and NMPA requirements as this is considered a change, although an editorial one rather than a content one.

Archiving Study Data

Thinking globally at the onset of development can help meet each agency's archival requirements in the long haul. The OECD does not reference a specific duration for archiving data, but rather leaves the decision to "appropriate authorities." However, both the U.S. FDA and NMPA provide detailed guidelines. The NMPA requires data archival five years after the drug is in market and specifically calls out terminated studies, requiring documentation of the reason and the data to be archived. On the other hand, the U.S. FDA states that it is necessary to archive for two years post-approval, five years post-IND submission, and two years post-study completion for non-submitted studies. The storage of study samples is always contingent on the viability of these items for possible future analysis.

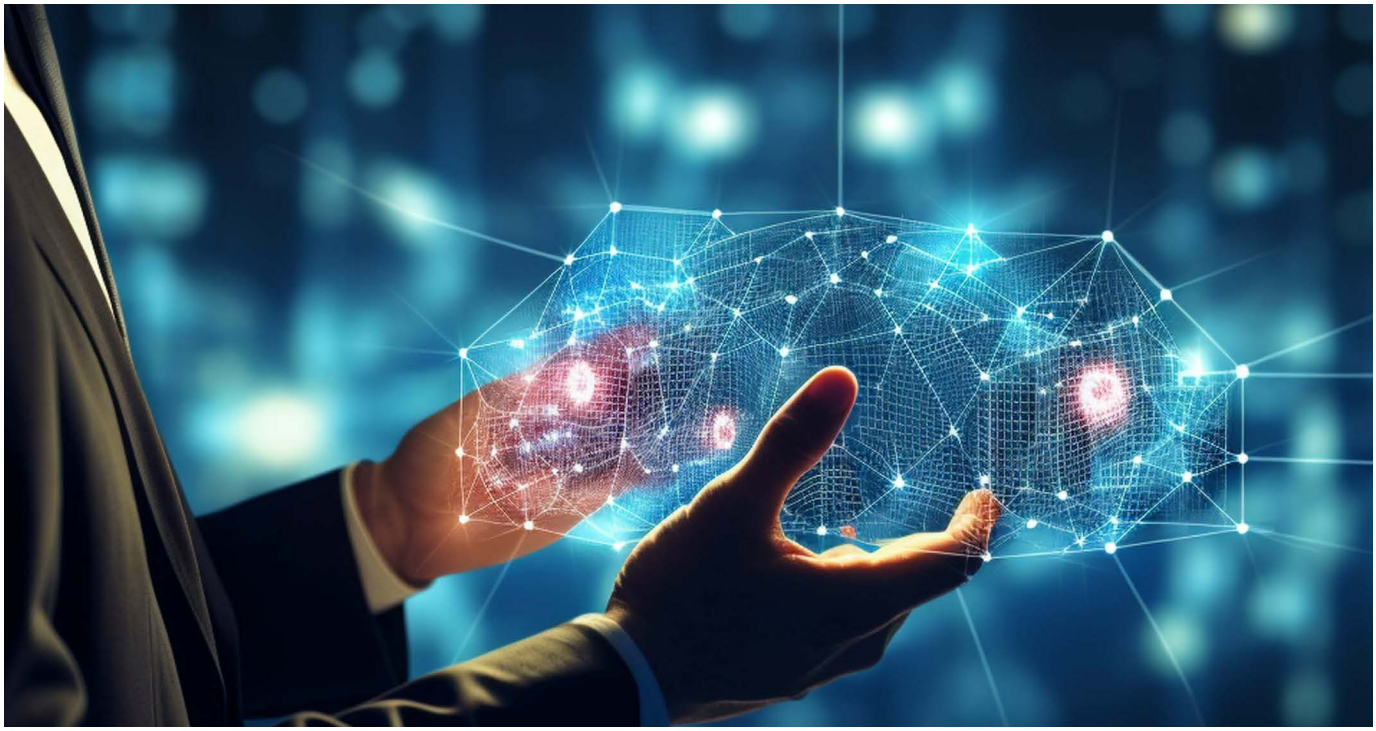
NAVIGATING THE COMPLEXITY

It can be challenging to navigate and manage all the regulatory requirements, but working with a laboratory testing partner can ease the process. Many laboratory testing partners provide expertise in preparing studies to file globally. Some also provide the full spectrum of inspection support, including translation services, regulatory planning and strategy, dossier preparation and communications with regulatory agencies, and submissions on the developer's behalf.

Drug developers approaching the application process must anticipate the agencies' differences and modify their applications to fit each submission. Often, filing IND packages for multiple global agencies can save time and money if regulatory variances are accounted for during study design, testing, reporting, and throughout the archival life cycle.

Allowing a testing partner to focus on these details can free up personnel to handle other pressing development responsibilities.

A laboratory's approach to designing preclinical studies can impact the test results, the scope of generated data, and overall assessment of safety—which means drug developers must keep these factors in mind when selecting a laboratory testing partner and making decisions about budgeting and program elements.

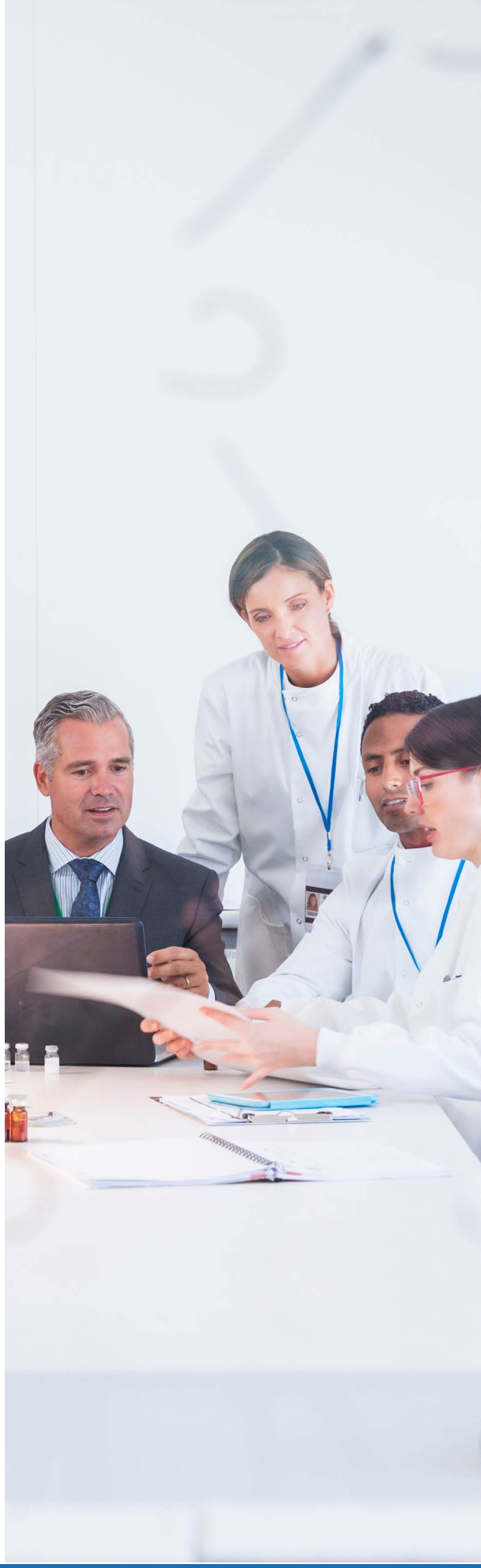


CHAPTER 3

PLANNING THE STUDY STRATEGY

The IND submission journey requires a multifaceted approach to testing, encompassing Drug Metabolism and Pharmacokinetic (DMPK) studies to unravel the drug's behavior within the body, preclinical toxicology assessments to meticulously examine its safety profile, and Bioanalytical (BAS) studies to quantitatively measure drug concentrations in biological samples.

Each of these core studies plays an integral role in shaping the regulatory narrative, providing crucial insights that guide subsequent clinical trials and contribute to the overarching goal of bringing safe and effective therapeutics to patients.



In this section, we delve into the key components of DMPK, toxicology, and BAS studies essential for a robust IND submission.

DMPK STUDIES

Drug Metabolism and Pharmacokinetic (DMPK) studies play a crucial role in IND submissions, providing valuable information about how a drug is metabolized and how it behaves in the body.

Core DMPK studies for IND submission typically include the following.

Bioavailability Studies

These studies measure the fraction of an orally administered drug that reaches the systemic circulation and is available for therapeutic action.

Drug-Drug Interaction (DDI) Studies

Assess potential interactions between the investigational drug and other commonly used drugs, providing insights into safety and efficacy when co-administered.

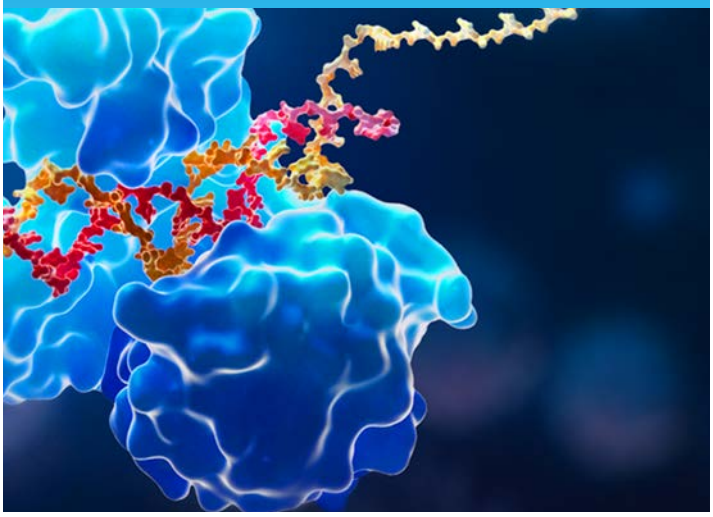
Pharmacokinetic (PK) Studies

PK studies evaluate the drug's concentration in the blood over time.

- **Single-Dose Studies:** Examine the drug's behavior after a single administration.
- **Multiple-Dose Studies:** Assess how the drug accumulates or is eliminated with repeated dosing.

Absorption, Distribution, Metabolism & Excretion (ADME) Studies

- **Absorption Studies:** Assess how the drug is absorbed into the bloodstream after administration (e.g., oral, intravenous).
- **Distribution Studies:** Examine the drug's distribution to different tissues and organs.
- **Metabolism Studies:** Investigate how the drug is metabolized in the body, including the identification of metabolites.
- **Excretion Studies:** Evaluate how the drug and its metabolites are eliminated from the body, often focusing on routes such as urine and feces.



Formulation Studies

Formulation studies evaluate the impact of different formulations (e.g., tablets, capsules) on the drug's bioavailability and pharmacokinetics.

The above DMPK studies provide critical data for understanding the drug's behavior in humans, guiding dosing recommendations, and ensuring safety in subsequent clinical trials. They contribute to the overall assessment of the drug's PK properties, helping regulators make informed decisions about its suitability for human use.

TOXICOLOGY STUDIES

Drug safety assessment is a broad, complex, and involved process that is essential to both the nonclinical and clinical phases of the development cycle. Before clinical trials can start, drug developers must define the drug's safety profile in *in vivo* studies—as well as a series of other IND-enabling studies. As clinical trials progress, toxicology studies are needed on a continuous basis. Then, a final set of tests is required for the New Drug Application (NDA).

But ensuring a successful clinical process starts with nonclinical toxicology studies. So, let's focus on the nonclinical (or preclinical) side of toxicology and what's required for IND applications. The specific safety assessment program depends greatly on the molecule type and clinical plan. However, there are five sets of tests that need to happen at baseline for nonclinical toxicology as per ICH M3(R2) guidance.

Here's a brief overview of each.

Pharmacology

Safety pharmacology studies define the profile of the molecule by assessing the potential for toxicity across major organ systems, including:

- CNS
- Cardiovascular
- Respiratory
- Gastrointestinal (not always required)
- Renal (not always required)

General Toxicology

General toxicology helps drug developers find the highest dose of the drug that can be given safely in clinical trials by studying the potential of the molecule to cause adverse effects after single or repeated exposure.

Typically, general toxicology studies start with a single dose and 14-day, 28-day, and 13-week studies to match or exceed the clinical dosing period.

Reproductive Toxicology

Reproductive toxicology studies assess the reproductive safety of a drug after repeated or chronic exposure.

These studies are conducted in three stages:

Segment I: Fertility and early-development-to-implantation

Segment II: Definitive embryo-fetal development

Segment III: Fetal/neonatal, peri/postnatal development

Genotoxic Studies

Genotoxicity studies assess the possibility of gene mutations or chromosomal abnormalities because of the candidate drug.

Toxicokinetic Studies

DMPK studies provide critical information for optimizing the drug properties of molecules early in the development process. These early PK studies evaluate the body's absorption, distribution, metabolism, and excretion (ADME) of a drug and can help screen the best drug candidate to move forward.

Toxicokinetic studies evaluate these characteristics under the conditions of the toxicology evaluations.

These studies are included in each general toxicology study as well as the reproductive toxicology studies to develop the PK and toxicokinetic profiles under longer dosing conditions to support the clinical plan.

BIOANALYTICAL STUDIES

Bioanalytical studies are essential for IND submissions, as they provide quantitative measurements of drug concentrations and their metabolites in biological samples.

Core bioanalytical studies typically include:

Method Development & Validation

Development and validation of analytical methods to quantify the investigational drug and its metabolites in biological samples (e.g., blood, plasma, urine). Validation ensures that the method is accurate, precise, and reproducible.

Assay of Drug Concentrations

Measurement of drug concentrations over time to confirm exposure and assess pharmacokinetics. Inclusion of assays for both the drug and any relevant metabolites.

Determination of Bioavailability

Assessment of the fraction of the administered oral dose that reaches the systemic circulation and is available for therapeutic action.

Bioequivalence Studies

Comparison of the pharmacokinetics of different formulations or routes of administration of the drug.

Drug-Drug Interaction (DDI) Studies

Investigation of potential interactions between the drug and other drugs that may be co-administered.

Assessment of Stability

Evaluation of the stability and compatibility of the drug in biological samples during collection, processing, and storage.

Immunogenicity Assays

Assessment of the immune response to the drug, particularly important for biologics. The formation of anti-drug antibodies (ADA) can inhibit the interaction of the drug with its intended target. This can affect efficacy of the drug as well as exposure. ADA formation does not necessarily translate to the clinic, but assessing it during preclinical studies is important to interpret toxicity/toxicokinetic data.

Determination of Maximum Tolerated Dose (MTD)

Identify the maximum dose of the drug that can be administered without causing unacceptable toxicity. These bioanalytical studies provide crucial quantitative data that contribute to the overall understanding of the drug's pharmacokinetics, bioavailability, and safety. Rigorous method development and validation ensure the reliability of the data generated, supporting the regulatory evaluation of the investigational drug for subsequent clinical trials.

PLANNING MATTERS

Putting together a strong IND submission starts with at least the critical studies outlined above. But planning an entire testing program and tuning it to a precise molecule, indication, and other parameters is equally as crucial.

Insufficient planning is one of the most common challenges for drug developers because of how variable each study program can be. In the next section, we'll review what kind of preparation should be expected to properly manage timelines and meet regulatory requirements.

CHAPTER 4

PREPARING FOR SUBMISSION

In order to initiate clinical trials for new therapeutics in the United States, drug sponsors must secure approval from the FDA. This authorization is pursued through the submission of an IND application, and once submitted, the development process comes to a halt until regulatory approval is granted.

The primary objective of an IND submission is to furnish regulators with data substantiating the safety of the product for human use.

What Does the FDA Look For?

The FDA diligently reviews each application within a 30-day timeframe to ensure that study participants are protected from an "unreasonable risk of significant illness or injury" during early clinical trials, and that the study design aligns with its objectives. INDs lacking sufficient support for safety claims may be subjected to a "clinical hold" until a comprehensive review is conducted.

Quarterly, the FDA receives approximately 200 new IND applications, totaling 777 applications between October 2020 and September 2021. While only about 9% of applications face clinical hold, this designation can swiftly derail a program. Successfully navigating the first major milestone, which is the IND submission, is crucial to safeguarding the program timeline. Particularly for drug candidates developed to address rare diseases or respond to widespread emergencies, delays due to clinical hold can have devastating consequences.

Achieving a successful IND submission demands strategic planning and meticulous timing. For drug sponsors unfamiliar with the necessary steps, there is assistance available, alleviating concerns in the process.

WHAT GOES INTO AN IND SUBMISSION?

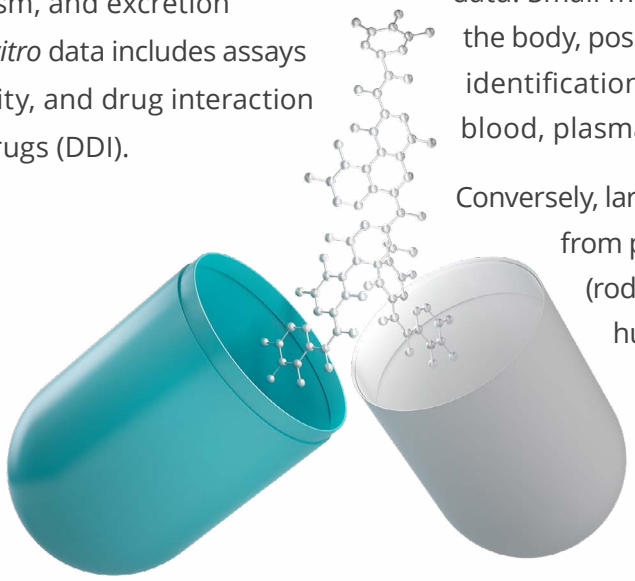
Regulators anticipate three essential sections in IND applications: preclinical testing data; chemistry, manufacturing, and controls; and clinical protocol or investigator information.

Preclinical Testing Data

Preclinical IND-enabling tests are conducted both *in vitro* and *in vivo*, aiming to address specific queries regarding therapeutic safety. For instance, DMPK studies characterize a drug's absorption, distribution, metabolism, and excretion (ADME) properties. *In vitro* data includes assays for stability, permeability, and drug interaction potential with other drugs (DDI).

in vitro & *in vivo*

The *in vitro* data aids researchers in refining a drug candidate's chemical structure, analyzing *in vivo* PK properties, and assessing its potential drug interactions in humans. *In vivo* studies typically involve test articles with PK properties closely mirroring those of humans. Studies used for metabolite identification, quantitative whole-body autoradiography (QWBA), and radiolabeled/non-radiolabeled mass balance generally yield the most valuable ADME data. For small molecules, metabolite identification is needed to select species for the toxicology program, based on which animals metabolize the drug similarly to humans.



Toxicology

Critical to the advancement of any IND submission is preclinical toxicology data. For small molecules, toxicology data are mandated from two species—rodent and non-rodent—in addition to genotoxicity data. Small molecules can form metabolites in the body, posing additional risks, necessitating identification through validated bioanalysis of blood, plasma, or other biological matrices.

Conversely, large molecules require data from pharmacologically relevant species (rodent and/or non-rodent), with non-human primates (NHPs) often being the pertinent species. Typically, large molecules do not necessitate genotoxicity data or metabolite identification. Safety pharmacology testing is also conducted to assess a drug's potential impact on the cardiovascular, pulmonary, and central nervous systems. For large molecules or oncology indications, safety pharmacology can be incorporated into the pivotal toxicology studies.

Dosing

Preclinical toxicology evaluations should encompass both single-dose and repeated-dose testing, and, when deemed necessary, include information on immunotoxicity and local tolerance. Additionally, regulatory authorities anticipate the provision of data related to reproductive and developmental toxicity as well as carcinogenicity following the completion of first-in-human (FIH) studies.

CMC

The second pivotal segment incorporated into an IND application pertains to Chemistry, Manufacturing, and Controls (CMC) data. These data play a critical role in ensuring the safety, efficacy, and uniformity of pharmaceuticals across different batches.

While drugs consist of an Active Pharmaceutical ingredient, they also encompass various solvents, chemical starting materials, inactive ingredients, etc., and it is imperative to evaluate and control the quality of these raw materials. For instance, drugs requiring sterile products must have a documented and validated sterilization protocol. Similarly, a molecule's inherent stability must align with the shelf -life information specified on a pharmaceutical label.

In essence, CMC data provide assurance to regulators that the identical product can be consistently manufactured with precise specifications. Furthermore, it serves as a demonstration of the developer's capability to optimize the manufacturing process and scale production from milligrams to kilograms and beyond.

Clinical Protocol

The final section of the IND submission, which regulators anticipate, is the clinical protocol and investigator information. This section holds vital details about each investigator participating in a clinical study. Among other particulars, the investigator statement must encompass information pertaining to each participating investigator's certifications, qualifications, and disclosure of financial arrangements.

A clinical protocol provides comprehensive details on trial design, patient selection criteria, clinical procedures, laboratory tests, and the measures to monitor the drug's effects on patients. It also necessitates the disclosure of investigators' experience with proposed primary endpoints. Any potential deviations from the trial design, including the collection and reporting of adverse effects, should be explicitly outlined in the clinical protocol.

Timeline

The process of conducting essential preclinical testing and compiling necessary investigator information for an IND application can span from as little as nine months to several years. Initiating the sequence with Chemistry, Manufacturing, and Controls (CMC) data is likely advisable, given its contribution to potential toxicity.

Subsequently, *in vivo* toxicity testing should follow, based on the clinical protocol. Submission delays can arise from various factors, with unexpected toxicity and the failure to generate a sufficiently large drug sample for the required tests being among the most common challenges.

IND APPLICATIONS FOR NEW VS. EXISTING DRUGS

Applications for IND vary between new and existing drugs, and the FDA has established specific pathways for each category.

505(b)(1) Pathway

This is the most comprehensive route for new drug development, commonly utilized for innovative drug candidates whose Active Pharmaceutical Ingredient (API) has not been previously studied or approved. The original drug sponsor is accountable for generating all necessary data and retains the right of reference for all information gathered during the investigation.

505(b)(2) Pathway

Introduced in 1984 to streamline drug development for rare diseases and prevent study duplication, this pathway is chosen when modifying a previously approved drug. "Modifications" encompass reformulating the drug or altering its route of administration, dosage, strength, or indication. This approach is accessible only if developers or sponsors demonstrate advancements to a previously approved drug. They may rely on published data or peer-reviewed articles, highlighting the drug's similarities to established molecules. Sponsors do not retain the right of reference under this pathway.

505(j) Pathway

Reserved for generic versions of existing drugs, this pathway requires drug candidates to be nearly identical in API, dosage, strength, administration route, labeling, quality, and intended use. Minor differences are acceptable, provided they do not necessitate additional data to support their use.

While these pathways may seem straightforward, selecting the appropriate one and generating the necessary *in vitro* and *in vivo* data for a drug candidate can be intricate. To gain insights into regulators' expectations for your IND submission, scheduling a pre-IND meeting is highly advisable.

SCHEDULING A PRE-IND MEETING

The primary objective of the pre-IND meeting is to address specific queries related to the initial U.S. first-in-human (FIH) study for new drugs and biologics, as well as other inquiries that could impact the IND application.

Getting Started

To initiate this process, a pre-IND meeting request should be directed to the appropriate Review Division responsible for overseeing products within the relevant therapeutic area of the IND application. The FDA's Office of New Drugs (OND) manages pre-IND consultations, making the critical determination of whether the benefits of a new drug outweigh its known risks. The OND provides guidance to drug sponsors on various aspects, including:

- The requisite data to substantiate the rationale for testing a drug in humans
- Designing nonclinical pharmacology, toxicology, and drug activity studies
- Initial drug development plans and regulatory requirements for demonstrating safety and efficacy
- Additional data requirements for IND applications

Pre-IND interactions commence with written comments, evolving into teleconferencing and, when necessary, in-person meetings. Sponsors should be aware that pre-IND meetings necessitate the submission of a briefing package. This package should encompass Chemistry, Manufacturing, and Controls (CMC), preliminary pharmacology, toxicology, Drug Metabolism and Pharmacokinetics (DMPK) data, and a clinical protocol that incorporates investigator information.

When to Schedule

Scheduling a pre-IND meeting stands as a pivotal and intricate step for drug sponsors. Strategic timing is crucial, and the meeting provides a unique opportunity for sponsors to engage with the FDA, addressing specific questions and ensuring a comprehensive IND application. A successful pre-IND meeting outcome is instrumental in averting clinical holds and minimizing errors during program development. Typically, the FDA responds within 21 days upon receiving the pre-IND request, and meetings are scheduled within 60 days of the request.

Consequently, sponsors should aim to submit their request approximately two months before the desired pre-IND meeting date. It's important to note that compiling the clinical protocol and investigator information demands extra time and resources, highlighting the intricate nature of the IND submission process.

CHAPTER 5

WORKING WITH A PARTNER

IND approval is imperative for any research involving human participants ingesting or applying a product. As illustrated, various regulatory pathways exist, each posing unique concerns contingent on the specific drug candidate.

The U.S. FDA's objective is not to complicate or mystify the application process but rather to guarantee the utmost safety of new drugs for human consumption. Drug sponsors who lack internal expertise in IND-enabling studies, and find navigating the evolving regulatory landscape challenging, may find value in collaborating with a laboratory testing partner.

To this end, sponsors should choose a partner that can fulfill all their testing needs (e.g., bioanalysis, toxicology, or DMPK) in-house and that has a proven track record for quality, accuracy, and detail.

Clear Communication

It's essential to select a full-service testing partner with an integrated communication management approach. Video chat capabilities, regular reporting, and using SEND data packages to compile relevant information in the format regulators prefer are crucial. Integrated communication can save time and reduce miscommunication when transferring documents between departments and testing sites.

Regulatory Relationships

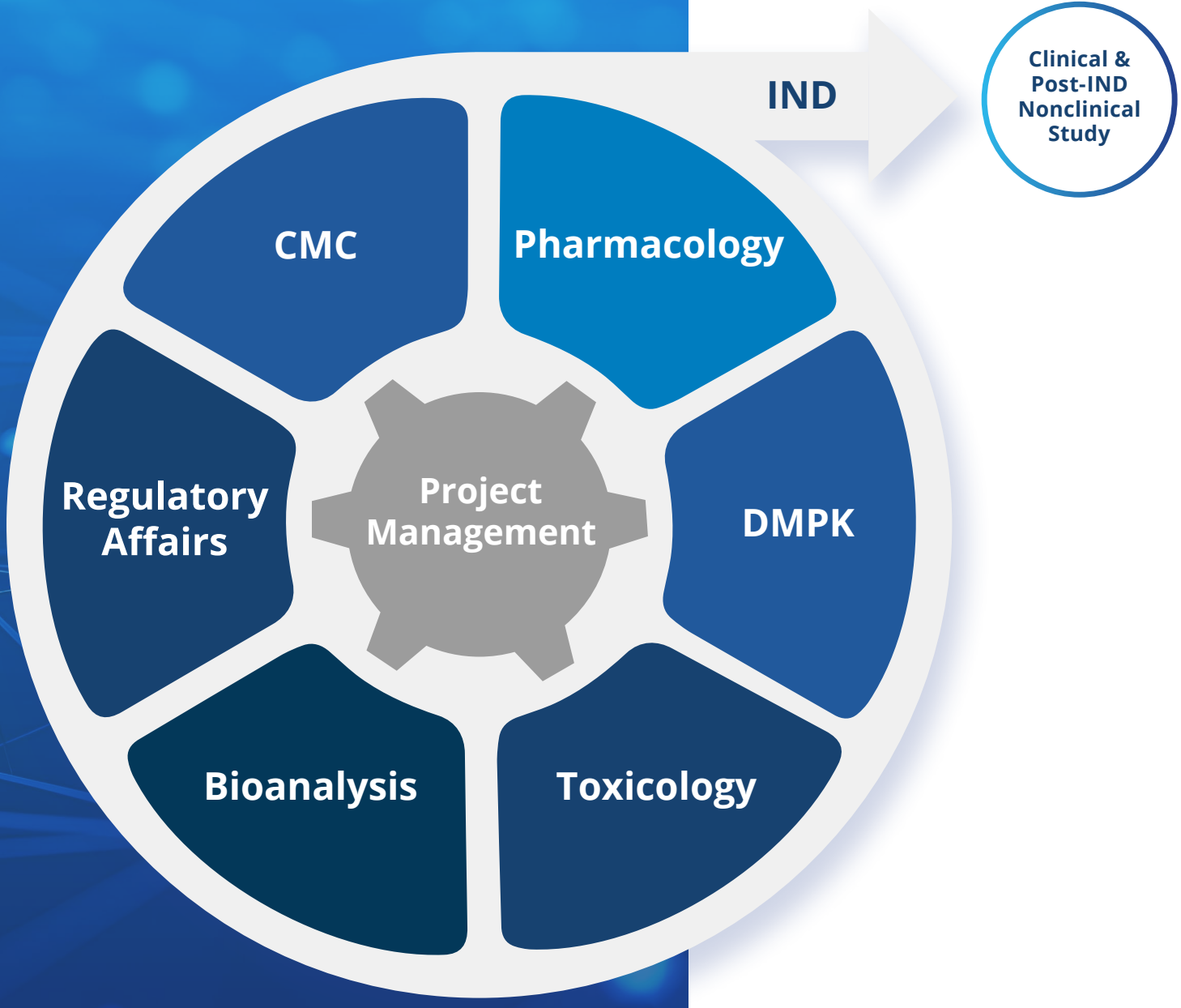
On the topic of regulators, make sure the partner has a strong reputation and collaborative relationship with regulatory bodies. They should also undergo frequent government inspections. Inquire about them and request results. Laboratory testing compliance with regulatory standards should be non-negotiable.

CLOSING THOUGHTS

Understanding and successfully navigating preclinical IND-enabling studies are vital steps in the drug development process.

This guide has covered essential aspects, from the role of IND-enabling studies in drug development cycles to the key components of an IND submission. We've explored the FDA's expectations, the importance of strategic planning, and the critical nature of pre-IND meetings. Additionally, we delved into the intricacies of different pathways for new and existing drugs, emphasizing the complexity of choosing the right route.

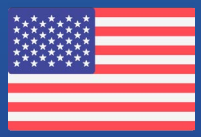
Lastly, we touched upon the potential value of collaborating with a lab testing partner. Overall, a thorough understanding of these elements is crucial for drug sponsors to navigate the regulatory landscape, ensuring the safety and success of new therapeutics in human trials.


IND
Clinical & Post-IND Nonclinical Study
CMC
Pharmacology
Regulatory Affairs
Project Management
DMPK
Bioanalysis
Toxicology

A WORLD-CLASS, GLOBAL PARTNER FOR IND TESTING & SUBMISSION

WuXi AppTec Laboratory Testing Division (LTD) provides a cross-functional team and range of services to support you from drug candidate selection to IND submission. It's everything a drug developer needs—flexible development options, compliance with global quality standards, and regulatory submission services—to make global IND filing convenient, efficient, and cost-effective.

- **1,000+** IND-enabling packages
- **500+** NDA-enabling packages
- **2,000+** molecules evaluated in pre-formulation studies
- **18,000+** *in vivo* studies/year
- **10,000+** tox studies/year
- **1M+** bio-samples analysis/year


U.S. FDA


NMPA


EMA


TGA

About WuXi AppTec Laboratory Testing

WuXi AppTec's Laboratory Testing Division is a comprehensive integrated testing platform supporting customers across the full spectrum of their development efforts to deliver innovative medicines to patients. From discovery through preclinical to clinical and beyond, we enable scientists to transform their ideas into healthcare products that ultimately improve life.

Improving Health. Making a Difference.