

Clinical trial application process: US

The approval to conduct clinical trials in the US is governed by the Investigational New Drug (IND) application process. Federal law states that to be shipped across state borders, a drug must be marketed (i.e., approved for market). In order for clinical studies to occur, for which non-marketed drugs are shipped to investigators potentially across the country, an exemption from this law is provided through the IND process.

An IND process is required to demonstrate that a drug is reasonably safe to use in humans and that it has pharmacological activity that justifies its use for specific indications. An IND application is required to conduct a study involving a non-approved drug or an approved drug in a non-approved indication, whether the study is conducted by a company or by an independent investigator.

The IND application contains information on:

- animal pharmacology and toxicology studies to determine if the product is reasonably safe for testing in humans
- manufacturing information to ensure the company can adequately produce and supply consistent batches of the drug
- clinical protocols and investigator information to assess whether the trials will expose patients to any unnecessary risks

After an IND is submitted, a sponsor or investigator must wait 30 days before initiating a trial in order for the Food and Drug Administration (FDA) to review the information.

Pre-IND consultation

Sponsors have an opportunity to meet with FDA staff who can provide guidance on the documentation required for an IND, and promote communication between the sponsor and the FDA on the proposed drug development plan. The FDA has suggested that formal meetings may occur prior to the filing of the IND (i.e., a pre-IND consultation), at the end of phase II studies to discuss phase III plans, and at the pre-NDA (New Drug Application) or pre-BLA (Biologic License Application) stage to discuss a marketing application.

There are no formal requirements on what to include in a pre-IND consultation package. Typically, brief information describing the drug together with a summary of the issues is submitted. Advice at the pre-IND consultation may be related to data needed to support the rationale for testing in humans, data requirements for an IND, initial drug development plans, and regulatory requirements for demonstrating efficacy and safety.

Data requirements

The amount of information that is required as part of an IND submission depends on the stage of development of the drug, the novelty of the drug, the known or suspected risks, and the extent to which the drug has been studied previously. The detailed requirements for an IND application are listed in the US Code of Federal Regulations (21CFR312.23), <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm>.

Exhibit 1: IND requirements

US IND requirements for a new chemical entity (NCE)

Part of submission	Contents
Cover sheet (FDA Form 1571)	<p>Name, address, telephone number of sponsor, date of application, name of investigational drug.</p> <p>Identification of phase of clinical investigation to be conducted.</p> <p>A commitment not to begin investigations until the IND is in effect.</p> <p>A commitment that an IRB* will be responsible for initial and continuing review and approval of the studies and the investigator will report to the IRB any changes in the study.</p> <p>A commitment to conduct the investigation according to all applicable regulatory requirements.</p> <p>Name and title of person responsible for monitoring the conduct and progress of the study.</p> <p>Name and title of person responsible for reviewing and evaluating information related to the safety of the drug.</p> <p>If a sponsor has transferred any obligations to a CRO**, the name and address of the CRO and what obligations have been transferred.</p> <p>Signature of person responsible (must be resident of US).</p>
Table of contents	
Introductory statement and general investigational plan	<p>Name of drug and all active ingredients, the drug's pharmacological class, the structural formula, formulation of dosage forms to be used, route of administration, broad objectives and planned duration of the study.</p> <p>Brief summary of previous human experience with the drug, with reference to other INDs if applicable, and to investigational or marketed experience in other countries that may be relevant to safety of proposed investigation.</p> <p>If the drug has been withdrawn from investigation or marketing in any other country for any reason related to safety or effectiveness, identification of the country and reasons for withdrawal.</p> <p>Brief description of investigational plan including rationale for drug or research study, indication to be studied, general approach used for evaluation of the drug, kinds of clinical trials to be conducted in the first year, estimated number of patients to be given drug in those studies, any risks of particular severity or seriousness anticipated based on animal toxicology results or prior studies in humans with the drug or related drugs.</p>
Investigator's brochure	<p>Brief description of drug substance and formulation.</p> <p>Summary of animal pharmacological and toxicology effects (and, if known, in humans).</p> <p>Summary of pharmacokinetics and biological disposition of drug in animals (and if known, in humans).</p> <p>Summary of safety and effectiveness in humans obtained from prior clinical studies.</p> <p>Description of risks and possible side effects to be anticipated on the basis of prior experience with the drug or related drugs and or precautions or special monitoring to be done as part of the investigation of the drug.</p>
Protocols	<p>Protocol for each planned study.</p>

	For phase I protocols, provide outline of investigation, number of patients planned, description of safety exclusions, description of dosing plan, elements of study that are critical for safety.
	For phase II and III, detailed protocols of all aspects of study should be submitted.
	Protocol is required to contain: statement of purpose and objectives of study; name, address and statement of qualifications of each investigator and sub-investigator; name and address of research facilities; name and address of IRB; patient inclusion and exclusion criteria and number of patients; description of design of study including control group and methods used to minimize bias; method for determining dose to be administered, planned maximum dosage, and duration of individual patient exposure to drug; description of observations and measurements to be made; description of clinical procedures, lab tests or other measures to monitor the effects of the drug and minimize risk.
Chemistry, manufacturing and control information	Emphasis for phase I studies should be placed on identification and control of raw materials and new drug substance. Final specs are not expected until the end of the investigational process.
	Information on drug substance and drug product.
	Information on composition, manufacture and control of any placebo used.
Labelling	Copy of all labels provided to investigator.
Environment analysis requirements	A claim for categorial exclusion or an environmental assessment.
Pharmacology and toxicology information	Adequate information about pharmacological and toxicological information from animals or <i>in vitro</i> . Pharmacology and drug disposition, toxicology, statement that study was conducted according to GLP (or reasons for non compliance).
Previous human experience	If drug has been marketed in US or other countries, details about that experience that is relevant to safety of the proposed investigation, list of countries where drug is marketed or has been withdrawn.
Additional information	Information on special topics, if applicable, such as drug dependence and abuse potential, radioactive drugs, pediatric studies, etc.
Relevant information	If requested by FDA, any other relevant information.

*IRB: Institutional review board

**CRO: Contract research organization

Source: Code of Federal Regulations, 21CFR312.23.

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>

Source: *Guidance for Industry. Content and Format of Investigational New Drug Applications (INDs) for Phase I Studies, Including Well-characterized, Therapeutic, Biotechnology-Derived Products*, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), November 1995.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071597.pdf>

FDA review

After a sponsor has submitted an IND, the FDA has 30 calendar days for review. The sponsor will receive a letter indicating an IND number and the name of the FDA project manager. After the review period, the investigational study may commence or the FDA has the option to put the file on *clinical hold*.^{*} If the sponsor has not been notified of any issues within the 30 days after the FDA receives the application, the study can start once institutional review board (IRB) approval is obtained. An IND is not “approved” by the FDA, but it is considered “in effect” unless the sponsor is notified otherwise before the end of the thirty-day review period.

^{*} *Clinical hold* is an order issued by the FDA to a sponsor to delay or suspend an investigation. It can be a *complete clinical hold* or a *partial clinical hold*. A complete clinical hold occurs when the delay or suspension of all clinical work is needed. If the FDA and sponsor agree to an alternate protocol during the initial thirty-day review period, this does not constitute a clinical hold. A partial clinical hold occurs when a delay or suspension is needed for part of the clinical work, but other parts are allowed to proceed.

When the FDA has concerns with an IND and issues a clinical hold letter, the specific reasons will be documented in the letter. Prior to issuing the letter, the FDA should attempt to resolve any identified issues with the sponsor. After a sponsor submits a complete response to a clinical hold letter, the FDA has a further 30 calendar days for review. If the sponsor’s response does not address all issues regarding the clinical hold, the sponsor is notified and the thirty-day clock does not restart until all issues have been addressed.

Protocol amendments

Updated information is required to be submitted to the FDA whenever a new protocol or a significant change in a protocol occurs, or if a new site or investigator is added. The FDA adds the information to the IND file and the changes can go into effect after approval by an IRB.

Any changes to the chemistry, manufacturing and controls section of the file are also required to be submitted to the FDA. As well, the FDA must be notified of any new animal pharmacology or toxicology information that may affect safety or efficacy, or if a decision is made to discontinue a trial.

Safety reports

The FDA must be notified without delay by phone or fax of unexpected fatal or life-threatening drug-related serious adverse events (SAE); this must occur no later than seven calendar days after the information of the SAE is received. The sponsor then has up to 15 days (i.e., a further eight days) to submit the written documentation. For serious and unexpected drug-related but non-fatal SAEs, the report must be submitted within 15 calendar days after the information is received.

Additional safety data from animal studies should also be submitted to the FDA within 15 days if it suggests a significant risk for humans.

Annual reports

Sponsors of an IND must submit an annual report with updated information on the product. It is required to be submitted within 60 days of the anniversary of the date the IND went into effect. The report should include:

- an update on each study under investigation, including patient enrolment and a brief description of any study results
- a summary of safety information including most frequent and serious adverse events, deaths, dropouts due to adverse events, understanding of the drug’s action, an update to pre-clinical studies, and significant manufacturing changes
- a general investigational plan for the coming year including the rationale for any study, indications to be studied, planned trials, estimated number of subjects, and anticipated risks
- an investigator’s brochure, if updated
- protocol modifications
- foreign market developments such as approval or withdrawal in any country