



When Execution Matters

Introduction to Clinical Trials February 22, 2010 – 10:40 am by Ven Thangaraj

This special edition of the Trianz blog will address a new industry: life sciences.

What is the clinical trials process?

A clinical trial is a medical research study designed to elucidate the efficacy, safety and additional information about a compound, device or biologic agent. Any given trial involves an experimental protocol, up to four phases, considerable expense in terms of time and money (up to 15 years and \$500 million) and many stakeholders who may be geographically dispersed. A clinical trial is “successful” if it results in regulatory approval for a product or if it enables researchers to eliminate (the earlier the better) products that display undesirable side effects or other negative characteristics. In some cases, the results of clinical trials can lead to uses of the drug, treatment or device that were not originally expected.

Before being tested on humans, the organization holding the rights to a promising compound performs a series of laboratory experiments to determine effects they are likely to encounter. It is during this preclinical stage, lasting about five years, that drug companies typically file and receive patents, which sets the patent clock ticking. From this data, the company determines whether it will pursue the lengthy and costly process of human testing. If it does, the company submits an investigational new drug (IND) application to regulatory authorities, which decides whether to grant approval for testing on humans.

An IND is a request for an exemption from the federal statute that prohibits an unapproved drug being shipped in interstate commerce. Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA; however, its main purpose is to detail the data that provides documentation that it is reasonable to proceed with human trials of the drug.

In addition to in vivo and in vitro data, the IND application will also typically include information pertaining to the composition, manufacture, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug. The application also includes detailed protocols for proposed clinical studies. These protocols are included to assess whether the initial trials will expose subjects to unnecessary risks. Also, information related to the qualifications of clinical investigators (professionals who oversee the administration of the experimental compound) is collected to assess whether they are qualified to fulfill their clinical trial duties.

Unless the FDA rejects an IND, the IND becomes effective 30 days following its receipt by the FDA. Once trials have commenced, the FDA may stop the trials by placing them on clinical hold status if concerns arise regarding the safety of the product.

Human Clinical Trials

Clinical trials are a highly regulated process designed to collect and analyze data to support claims concerning the safety and efficacy of a product. Clinical trials involve the administration of the study drug to healthy human volunteers or patients under the supervision of a qualified investigator, usually a physician, pursuant to an FDA-reviewed protocol.

Human clinical trials typically are conducted in three sequential phases, although the phases may overlap. Clinical trials must be conducted under protocols that detail the objectives of the study, as well as the parameters to be used to monitor the safety and efficacy criteria being evaluated. Each protocol must be submitted to the FDA as part of the IND. Each clinical trial must be conducted under the auspices of an Institutional Review Board (IRB) that

considers, among other factors, ethical factors, the safety of human subjects, the possible liability of the institution, and the informed consent disclosure that must be obtained from participants in the clinical trial.

Although the goal of a clinical trial is to obtain safety and efficacy data, the overriding consideration in the study is the safety of the participants. The FDA monitors the study design and the conduct of clinical trials to ensure that subjects in the trials are not exposed to unnecessary risks.

Phase I

Phase I clinical trials represent the initial administration of the investigational drug to a small group of healthy human subjects or, more rarely, to a group of selected patients with the targeted disease or disorder. Certain drugs are administered to the targeted population only (healthy individuals are excluded) due to ethical constraints relating to drug toxicity and benefit versus risk.

The goal of Phase I clinical trials is typically to test for safety, dose tolerance, absorption, bio-distribution, metabolism, excretion and clinical pharmacology and, if possible, to gain early evidence regarding efficacy. The total number of subjects included in Phase I studies varies with the type of drug being investigated, but is generally in the range of 10 to 40.

Phase II

Phase II clinical trials involve a small sample of the actual intended patient population and seek to assess the efficacy of the drug for specific targeted indications, to determine dose response and the optimal dose range, and to gather additional information related to safety and potential adverse effects. Phase II studies typically are closely monitored and conducted with a relatively small number of patients, usually involving 60 to 200 subjects. Phase II lasts on average two years.

Phase III

Phase III clinical trials are initiated to further establish the clinical safety and efficacy of the investigational drug in a broader sample of the general patient population. The studies are conducted at geographically dispersed study sites with patients who suffer from the target disease or disorder, to obtain definitive statistical evidence of the efficacy and safety of the proposed product and dosing regimen.

Trial size differs depending on the disease being addressed, and trials often are designed to accommodate factors such as statistical significance and avoiding bias. Phase III studies usually include 100 to several thousand people. About three to four years elapse before the pharmaceutical or biotechnology company can accumulate enough data to validate these experiments.

If the Phase III data is positive, the company files a new drug application (NDA), a document that contains data to support the safety and efficacy of the drug. Regulatory authorities, such as the U.S. Food and Drug Administration (FDA), review the NDA and decide, usually within two years of the application, whether to grant approval for the sale of the drug. If the drug is approved, the company can market and distribute the drug.

Phase IV

Phase IV or post-market surveillance studies are conducted after a drug / device has received marketing approval from the regulators and is being sold to the public. Studies in this phase address such issues as differential effects in various populations and side effects resulting from long-term use. Phase IV studies are usually long term studies that can last over 15 years and enroll hundreds of thousands of patients. These studies can also identify additional uses for the drug and can result in the sponsor submitting a supplemental new drug application (sNDA).

The New Drug Application (NDA) Filing

The new drug application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale in the U.S. All data obtained from a comprehensive development program, including research and product development, manufacturing, preclinical and clinical trials and related information, are submitted in an NDA filing to the FDA and the corresponding agencies in other countries for review and approval.

In addition to reports of the trials conducted under the IND, the NDA includes information pertaining to the preparation of the new drug or antibiotic, analytical methods, details of the manufacture of finished products and proposed product packaging and labeling. Although the FDC Act requires the FDA to review NDAs within 180 days of their filing, in practice, more time may be required. The FDA also frequently requests that more information be submitted, requiring significant additional review time.

At the conclusion of the FDA's review of an application, three possible action letters can be sent to the NDA's sponsor:

- Not Approvable Letter: Lists the deficiencies in the application and explains why the application cannot be approved.
- Approvable Letter: Signals that, ultimately, the drug can be approved. Lists minor deficiencies that can be corrected, often involves labeling changes, and possibly requests a commitment to do post-approval studies.
- Approval Letter: States that the drug is approved. May follow an approvable letter, but also can be issued directly.

If the FDA issues either a "not approvable" or "approvable" letter, it provides the applicants the opportunity to meet with the agency and discuss the deficiencies. The purpose of the meeting is to discuss what further steps are necessary before the application can be approved. Once the FDA signs an approval action letter, the product can be legally marketed in the U.S. starting that day.

Fast Track, Priority Review, and Accelerated Approvals

Fast track is a formal mechanism to interact with the FDA using approaches that are available to all applicants for marketing claims. The benefits of fast track include scheduled meetings to seek FDA input into development plans, the option of submitting an NDA in sections rather than submitting all components simultaneously, and the option of requesting evaluation of studies using surrogate endpoints. The fast track designation is intended for the combination of a product and a claim that addresses an unmet medical need, but is independent of priority review and accelerated approval. An applicant may use any or all of the components of fast track without the formal designation. Fast track designation does not necessarily lead to a priority review or accelerated approval.

Priority review is a designation for an application after it has been submitted to the FDA for review for approval of a marketing claim. Reviews for new drug applications are designated as either standard or priority. A standard designation sets the target date for completing all aspects of a review and the FDA taking an action on the application (approve or not approve) at 10 months after the date it was filed. A priority designation sets the target date for the FDA action at six months. A priority designation is intended for those products that address unmet medical needs.

Accelerated approval regulations apply to products used in the treatment of serious illnesses that appear to provide meaningful therapeutic benefits over existing treatments. These regulations permit approval of such products before clinical research is completed based on the product's effect on a clinical endpoint or surrogate endpoint. When a product is approved under the accelerated approval regulations, the sponsor may be required to conduct additional well-controlled studies to verify that the effect the surrogate endpoint correlates with improved clinical outcomes or to otherwise verify the clinical benefit. In the event such post-marketing studies do not verify the drug's anticipated clinical benefit or if there is other evidence that the drug product is not shown to be safe and effective, expedited withdrawal procedures permit the FDA, after a hearing, to remove a product from the market.

Who Is Involved in a Clinical Trial?

Clinical trials involve many organizations and roles:

- *Sponsors*: These are the entities that initiate and pay for the trial. Sponsors may include life sciences organizations (LSOs) – pharmaceutical companies, biotechnology companies or medical device companies, government agencies (e.g., such as the National Institute of Health (NIH) or the U.S. Army), physician-investigators, healthcare organizations and institutes.
- *Contract Research Organizations (CROs)*: These are proxy research representatives that sponsors may contract with to administer the trials.
- *Site Management Organizations (SMOs)*: These are independent clinical trial offices that manage investigative sites.
- *Research Institutes*: These are the sites where clinical trials take place, usually hospitals, universities, doctors' offices or community clinics. These investigative sites can be private, public or government-owned. Often, a clinical trial is conducted by multiple facilities working collaboratively.
- *Principle Investigator*: Typically, this is the scientist who initiated the clinical trial and was primarily responsible for the preclinical studies that established the scientific validity of the current clinical trial.
- *Clinical Researchers*: These can include physicians, Ph.Ds, nurses, social workers and others in the clinical environment. Their backgrounds and experience levels can vary considerably. For some of these individuals, clinical trials provide a significant portion of income.
- *Clinical Research Associates (CRAs)*: These individuals are part of the investigating team and provide

services such as laboratory, data collection and analytical support.

- *Collaborative groups*: These are groups of researchers who play different roles depending on the group, its sources funding and its objectives. Collaborative groups may provide site management functions, access to research institutes, find or provide trial sponsorship or have a CRO role, depending on the trial.
- *Patient / Participants*: These are human volunteers of a clinical trial. These volunteers may be paid or unpaid, healthy or ill, depending on the role they play. The participants are often geographically diverse.
- *Research Ethics Boards (REBs)*: These are independent groups of physicians, statisticians, academics, community advocates and others whose mandates are to protect the rights of the trial's participants and to ensure the trial is conducted in an ethical manner.