

Fifth Edition

First Principles of Gastroenterology

The Basis of Disease and an Approach to Management

5



JANSSEN-ORTHO

*A.B.R. Thomson and
E.A. Shaffer, editors*

3

Pharmaceutical Research and Clinical Trials: The Basis for New Knowledge

B.G. Feagan and A. Archambault

1. INTRODUCTION

The development of new drugs is an important research activity that requires close cooperation between academic investigators, the pharmaceutical industry and regulatory authorities. Since 10 to 15 years of investment is often required before a product reaches the market, and only one out of 8,000 substances initially tested in animals results in a marketable drug, this activity is both time-consuming and expensive. Despite the relatively small size of the Canadian pharmaceutical market (3% of global drug expenditures), Canadian investigators have played a leading role in the development of several new treatments for gastrointestinal diseases. The goal of this chapter is to familiarize the reader with the activities that are necessary for successful drug development.

2. CLINICAL RESEARCH REGULATIONS AND SUPERVISION

Investigators, sponsors and institutional authorities share equal responsibility for producing high-quality data and following ethical recommendations for the conduct of biomedical research involving human subjects. The Declaration of Helsinki, first proposed in Finland in 1964 and most recently revised by the World Medical Assembly in South Africa in 1996, is a universally accepted ethical code which researchers must follow. The central philosophy behind the declaration is respect for the rights and safety of the individual.

The technical requirements for good clinical research practices are stipulated in a document entitled Good Clinical Practice (GCP): Consolidated Guidelines, issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). These guidelines were officially adopted by Health Canada in 1997. In

accordance with these standards, the Medical Research Council of Canada (MRC) has also specified guidelines for research involving human subjects.

In the United States, federal regulations concerning the development of new drugs and their subsequent admissibility for clinical investigation were enacted in 1938. Following the tragic events surrounding the use of thalidomide in the 1950s, important amendments were adopted. These included a new requirement for extensive review of preclinical data and a requirement to obtain informed consent of participants in clinical studies. The reporting of preclinical findings became mandatory in 1962. In an attempt to standardize compliance with regulatory requirements, good clinical practice (GCP) guidelines for sponsors (1977) and for investigators (1978) have been defined. These guidelines clearly specify the roles and responsibilities of the clinical research team. Although some differences exist among countries in the regulations governing clinical research in humans, in recent years these guidelines have become more uniform. A comprehensive set of guidelines for drug trials emerged in October 1990 as a result of a meeting where good practice guidelines were compared by scientists from the European Community and North America. Uniform standards were subsequently defined that have become the current gold standard for conducting clinical research.

3. CLINICAL DRUG DEVELOPMENT

The research process includes preclinical studies, clinical trials and, in the post-market phase, observational studies.

3.1 Preclinical Studies

The pharmaceutical industry identifies chemical structures for synthesis and then evaluates the biological effects of these compounds using *in vitro* and animal models. Compounds that show promise are selected for further study. This phase of drug development was historically performed using labor-intensive “high through-put” screening, in which large numbers of chemical compounds are tested for activity in a model assay. More recently, the development of computer programs that identify candidate molecules based on their 3-dimensional structure and likelihood of interacting with a candidate receptor has accelerated the process. Furthermore, molecular engineering techniques have produced “biologics” such as monoclonal antibodies that are highly specific for a given target, substantially shortening the preclinical development process.

Preclinical studies are usually conducted in the research laboratories of pharmaceutical companies or in university centers. Once a potential compound has been identified, pharmacological experts analyze the main biological

effects of the drug, the duration of action and the adverse effects of the compound in various animal species. Pharmacokinetic studies performed in animals define the absorption, volume of distribution, metabolism and excretion of the candidate compound. These studies are integral to the development of initial human experiments. Extensive toxicological studies are performed to identify possible mutagenic or teratogenic effects of the candidate drug. Compounds that meet the requirements of these early studies are further assessed to determine the optimum dose and route of administration. Based on the results of these studies a drug may be selected for further development. This process frequently takes two to four years.

Subsequently a submission is made to regulatory authorities for authorization to administer the potential new drug (IND: investigational new drug) to humans. The process of regulatory review is a well-defined procedure that usually takes one to two months. During this time the preclinical data are assessed by an appropriate national regulatory body, such as the U.S. Food and Drug Administration (FDA) or the Therapeutic Product Division of Health Canada. International regulatory agencies follow similar procedures, and for this reason multi-center studies are often performed using integrated protocols. Regulatory review evaluates the preclinical data for safety and scientific validity, ensures that the manufacturing process is safe, and determines if the clinical development plan is appropriate.

3.2 Clinical Trials

Although the distinctions are somewhat arbitrary, four phases of clinical drug development are generally recognized.

3.2.1 PHASE I

These studies are carried out in small numbers of individuals, who are usually normal, healthy volunteers. The primary objective is to evaluate safety and tolerability and to obtain an initial pharmacokinetic profile. These studies are initially performed with a single drug dose, then with multiple doses.

Pharmacokinetic and pharmacodynamic studies in humans must be performed with close medical surveillance and continuous monitoring of patients for adverse effects. During the time that Phase I studies are underway, animal studies for toxicity and potential carcinogenicity are continued.

3.2.2 PHASE II

At this phase, pilot studies to evaluate the efficacy and safety of a new drug are performed in *patients with the specific disease of interest*. The studies are usually short-term and may either be placebo-controlled or compare the candidate compound to a standard therapy. The emphasis in Phase II is on

identification of the most appropriate dose, dosing interval and route of administration. These studies provide data that is essential for the design of Phase III trials. The latter studies definitively evaluate efficacy. Long-term toxicity and carcinogenicity testing in animals continues during this phase.

3.2.3 PHASE III

These studies, which are usually conducted in a relatively large number of patients, are designed to demonstrate either short- or long-term efficacy and provide further safety data. A Phase III trial usually compares a fixed dose of the new drug to conventional therapy under conditions that approximate those of usual clinical care. The therapeutic profile of the drug is defined by the results of these studies, which determine the final indications, dosage, route of administration, contraindications, adverse effects and possible drug interactions. Usually two independent and adequately controlled Phase III studies with positive results are necessary for regulatory approval.

The duration of Phases II and III is often in the range of three to five years. Following accumulation of appropriate Phase III data, a submission to regulatory authorities is filed (NDS: New Drug Submission). These data are then scrutinized by the appropriate government experts. In Canada it may require up to two additional years before approval to market the product is received.

3.2.4 PHASE IV

Following approval for general use, the evaluative process continues. Clinical studies are performed with approved or marketed drugs to gather more information on possible adverse events, to compare them with alternative treatments, and to detect interactions with other drugs. Due to the low prevalence of most serious adverse events, Phase IV observational studies (post-market surveillance) are often the only means of adequately defining the safety profile of new compounds. New information regarding safety may result from spontaneous reporting of adverse events by physicians or through observation of specific groups of patients in prospectively defined registries. During this period, new indications, new formulations or effective combinations of the new drug with existing therapies may be explored. The knowledge of a new pharmaceutical grows gradually through the various phases of clinical research, and it is never 100% complete. All relevant findings must be documented and reported, regardless of the time that has passed since the initial approval of the drug for general use.

4. METHODOLOGY IN CLINICAL RESEARCH

The randomized, controlled trial is the benchmark for the evaluation of new

drug therapies. Random allocation is a powerful means of controlling for the potential effects of confounders and serves to minimize bias (systematic deviation from the truth) on the part of physicians and patients. Concealing the treatment allocation from the patient and investigator (blinding), which reduces the potential for bias, is also a fundamental component of a rigorously designed clinical trial. Considerable controversy has arisen regarding the use of placebo controls in evaluating new drugs. Some authors have argued against their use on the basis that patients are denied treatment of proven efficacy and thus may experience some degree of morbidity by participation in a placebo-controlled study. However, a placebo comparison allows an evaluation of the new therapy against the alternative of no treatment, and thus is scientifically valid and ethical when the standard therapy has only modest efficacy or causes important adverse effects. In Phase III trials it is vital that investigators choose a clinically meaningful outcome as the primary measure of response. In the past there has been an over-reliance on surrogate markers of efficacy such as improvements in laboratory tests. In some instances these measures did not correlate with clinically meaningful events. Investigators should also consider utilization of patient-reported outcomes, such as quality of life measures, in addition to the more conventional clinical trial outcomes of death, occurrence of disease-related complications and clinical activity indices.

Once an appropriate outcome is identified, the planning of a clinical trial requires input from a biostatistician. Careful consideration is given to the number of patients required, which is dependent upon the alpha (false positive) and beta (false negative) error rates selected by the investigator, the size of treatment effect considered clinically meaningful and the estimated rate of occurrence of the outcome of interest in the placebo (or standard therapy) group. If interim analyses are planned, these must be defined prior to initiation of the study, and appropriate statistical techniques must be employed to account for the increase in the alpha error rate that results from the use of multiple statistical testing.

5. PLANNING A CLINICAL TRIAL

5.1 Protocol Design and Implementation

The study protocol should explicitly state the rationale for studying the drug in the disease of interest. The source and chemical nature of the compound, its pharmacology and toxicology, and the data obtained in previous clinical investigations must be present in appropriate detail. All study protocols must be approved by the appropriate regulatory authorities. The objectives of the study must be clearly stated and appropriate methodology employed to ensure that these are met. The study treatment schedule should define the drug administration (dosage, strength, route of administration, the blinding process, packaging and labeling) in sufficient detail.

The inclusion and exclusion criteria, baseline, pre- and post-treatment measurement and evaluation visits and procedures for reporting adverse events and treatment overdoses must be clearly specified.

A study discontinuation procedure is defined in the event of lack of efficacy, intolerable side effects, poor patient compliance or the occurrence of a treatment endpoint.

Detailed definitions of the statistical analysis, data management procedures, administrative structure of the study and insurance and liability requirements are also necessary.

The protocol should contain a description of the background information that is provided to the patient and the informed consent document. For the patient's protection, lay language must be used. Diary forms and informed consent papers must be translated into the patient's primary language.

Once a protocol has been developed, an appropriate administrative structure should be organized. An executive (steering) committee is constituted, which is responsible for the strategic aspects of conducting the trial. Usually other committees are organized to oversee the operational aspects of the trial, to monitor the safety of participants, and to adjudicate key outcomes.

5.2 Selection of Investigators and Centers

The selection of the investigators for clinical research will depend on the nature of the drug and the phase of the investigation. Experts in clinical pharmacology are selected for Phase I and II studies; experts in medical practice or medical specialties will usually be selected for Phase III and IV studies.

The principal investigator in each center is responsible for the study in accordance with the protocol and for the accurate and complete reporting of the results: he or she must sign a formal statement of agreement for the study and its commitments and provide copies for the sponsor and government authorities. Investigators are selected on the basis of several criteria, including their past record in peer-reviewed medical research, their current interest in the proposed study and available time to participate. Appropriate on-site hospital or private clinic facilities with adequate space, equipment, safe drug storage, assistance from a research nurse and access to a certified laboratory are essential prerequisites for participation in clinical trials. The laboratory must be able to conduct the study according to the guidelines of good laboratory practices (GLP) adopted by the FDA in 1978. In addition, the investigators should be able to make an estimate of the number of study subjects available at their centers so a recruitment projection can be derived. The investigators must agree to have their facility and data audited at any time by the sponsor's representatives or by the regulatory authorities (FDA or TPP).

6. INFORMED CONSENT FORM AND ETHICAL ISSUES

The informed consent form is a written description of the nature and purpose of the trial. This document includes an explanation of the nature of randomization and includes a description of the benefits, foreseeable risks, discomforts and potential side effects of participating in the study. The consent form should inform the patient that he or she has the right to withdraw from the study at any time without prejudice, and that alternative treatments are available, should he or she decide not to participate in the study. The consent form is presented to the patient, preferably in the presence of an impartial witness, by the investigator or a qualified delegate; sufficient time must be allowed for the patient to consider the information and to ask questions.

This form is an acknowledgment that specific information has been given; it is never proof that the subject has been fully informed. It does not indicate the degree of comprehension or autonomy of the patient. Even if the informed consent is for the protection of the investigator and the patient, it has no legal power in North America.

7. CLINICAL MONITORING

An essential aspect of the conduct of clinical research is monitoring. All aspects of these investigations must be open and verifiable upon independent audit.

Accountability for drug dispensal to patients includes surveillance of the expiry date, lot numbers, stability and storage conditions. Compliance with the study medication requirements should be assessed by direct questioning and/or pill counts. All unused medication should be returned to the investigator.

The patient's condition before, during and after the treatment period, laboratory data, concomitant therapy, and adverse events should be accurately recorded using standardized procedures at specified times. Information that is recorded in the case report form should be consistent with information documented in the patient's medical record. Principles of good clinical practice (GCP) should be followed. The number and extent of audits will vary from study to study, depending upon specific requirements.

At the completion of the study, an adjudication committee undertakes the final evaluation of data for both efficacy and safety. This committee ensures the accuracy, completeness and legibility of the data. Finally, the results and conclusion of the study are summarized in a final report, which the investigators must review and sign. Publication of the data in a peer-reviewed medical journal follows.

8. INSTITUTIONAL REVIEW COMMITTEE (IRC)

No patient can be enrolled in a clinical trial before an institutional review committee has accepted the protocol and the informed consent form.

During this process, the scientific aspects of a trial are evaluated by experienced clinical researchers in each institution where the study is performed. Modifications to the protocol suggested by the IRC should be carefully considered by the investigators.

The committee should comprise at least five sufficiently qualified members, both sexes must be represented and members should be sensitive to local racial and cultural issues. There should be at least one nonscientific member and one member who is not affiliated with the institution. There should be no conflicting interests for any of the committee members.

The elements of the informed consent to be considered by the members of the committee are numerous. These are specifically outlined in the Declaration of Helsinki and in the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (August 1998), governing research funding in Canada.

Confirmation of acceptance of a study by the IRC must be transmitted with the signed agreement form to the government authorities.

9. REPORTING THE RESULTS OF CLINICAL RESEARCH

Publication of findings in a high quality peer-review journal should be the aim of all clinical research. Although the peer review system has been repeatedly criticized on the basis of subjectivity and inconsistency, no reporting system alternative exists that meets the needs of both researchers and the public. Publication of the findings of a clinical trial in a top tier journal such as the *New England Journal of Medicine* or the *Lancet* has enormous influence on clinical practice. Accordingly editors and reviewers for these publications have a shared responsibility to protect the public from flawed or biased research.

10. CONCLUSION

The efficacy and safety of a drug must be well established by appropriate therapeutic trials before it can be accepted for clinical use. Internationally accepted regulatory standards, scientific principles of clinical trial design and good clinical practice rules have evolved to meet these requirements. This chapter should provide the medical student with some basic information concerning drug development and with a better understanding of this important area of clinical research.

BIBLIOGRAPHY

- Canada. Health Protection Branch, Health Canada. Drugs Directorate guidelines.
- Clinical trial review and approval (March 1997).
 - Preparation of human new drug submissions (1991).
 - Conduct of clinical investigations. Catalogue no. H42-2/14 (July 1989).
- Canada. Medical Research Council of Canada. Guidelines on research involving human subjects. Minister of Supply and Services Canada, 1987. Catalogue no. MR 21-5/1987E.
- The clinical trial in Canada, USA, in Nordic and EEC countries. 2nd Symposium on drug development sponsored by the Faculty of Pharmacy of the Université de Montréal and the Health Protection Branch, Canada, May 6-7, 1990, Montréal, Québec. Montréal: Université de Montréal, 1990 (binder).
- Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects.
- France. Ministère des affaires sociales et de l'emploi. Ministre chargé de la santé et de la famille. Bulletin officiel. Direction des journaux officiels, 26, rue Desaix, 75105 Paris, France.
- Good clinical practice: consolidated guideline. ICH harmonized tripartite guideline, adopted by the Therapeutic Products Directorate of Health Canada. Catalogue no. H42-2/67-11-1997E.
- Good Clinical Research Practices Limited. Clinical study monitoring (binder).
- Three-day course presented in Mississauga, Ontario, March 1991.
- Bolaychuk WP, Ph.D.; Ball GT, C.D., Ph.D.; Kimpton DJ.
- European office: Round Windows, Grayshott Road, Headly Down, Hampshire, U.K. GU 358KJL
- Review articles. Drug Information Journal (January/June 1982):7-96.
- Emanuel EJ, Miller FG. The ethics of placebo-controlled trials – a middle ground. N Engl J Med 2001; 345(12):915-919.
- Good Clinical Practice: Consolidated Guideline. Health Canada.
- Website: www.ncehr-cnerh.org
- From Test Tube to Patient: New Drug Development in the United States. Second Edition January 1995. FDA USA Food and Drug Administration.
- Website: www.fda.gov/fdac/special/newdrug/ndd_toc.html
- Spilker B. Guide to clinical trials. Philadelphia: Lippincott Williams and Wilkins, 1991.
- Good Clinical Practice in FDA-Regulated Clinical Trials. Website: www.fda.gov/oc/gcp/default.htm