

# GLOSSARY

## ***15-Day Reports:***

Postmarketing adverse experience report for all AEs that are both serious and unexpected must be reported within 15 calendar days to FDA. These 15-Day Alert reports are also referred to as MedWatch Reports and are reported to FDA on an FDA 3500A or MedWatch Form.

## ***Abbreviated New Drug Application, or ANDA:***

Acronym for Abbreviated New Drug Application

A simplified submission permitted for a duplicate of an already approved drug. ANDAs are for products with the same or very closely related active ingredients, dosage form, strength, administration route, use, and labeling as a product that has already been shown to be safe and effective. An ANDA includes all the information on chemistry and manufacturing controls found in a new drug application (NDA), but does not have to include data from studies in animals and humans. It must, however, contain evidence that the duplicate drug is bioequivalent to the previously approved drug.

## ***Accelerated Approval:***

A highly specialized mechanism intended to speed approval of drugs promising significant benefit over existing therapy for serious or life threatening illnesses. It incorporates elements aimed at making sure that rapid review and approval is balanced by safeguards to protect both the public health and the integrity of the regulatory process. This mechanism may be used when approval can be reliably based on evidence of a drug's effect on a "surrogate endpoint", or when FDA determines an effective drug can be used safely only under restricted distribution or use. Usually, such a surrogate can be assessed much sooner than such an endpoint as survival. In accelerated approval, FDA approves the drug on condition that the sponsor study the actual clinical benefit of the drug.

## ***Action Letter:***

An official communication from FDA to an NDA sponsor that informs of a decision by the agency. An approval letter allows commercial marketing of the product. An approvable letter lists minor issues to be resolved before approval can be given. A not approvable letter describes important deficiencies that preclude approval unless corrected.

## ***Active/Active Substance:***

Term used in the screening phase of drug discovery. An "active" is a substance that inhibits or stimulates at the concentration run in a screen, thereby indicating the substance may have pharmacological effect.

## ***ADME:***

Acronym for absorption, distribution, metabolism, and elimination. ADME studies are used to determine how a drug is taken up by the body, where it goes in the body, the chemical changes it

undergoes in the body, and how it is eliminated from the body. ADME studies are performed preclinically in animal models, and in the clinical development of a compound. ADME studies describe the pharmacokinetics and bioavailability of a drug compound.

### ***Adverse Experience (AE):***

An AE is defined as any unfavorable and unintended sign (including significant abnormal laboratory findings), symptom, or disease temporally associated with the use of study treatment(s) during a clinical study, whether or not considered related to the use of the study treatment(s).

An AE includes:

- Conditions which appear after initial administration of the study treatment(s)
- Pre-existing conditions which are present prior to the study treatment(s) and worsen after the administration of study treatment(s)
- Any historical conditions not present prior to initiation of study treatments, which reappear following the administration of study treatment(s)

### ***Adverse Drug Experience (ADR):***

Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice, an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring during drug withdrawal; and any failure of expected pharmacological action.

### ***Advisory Committee:***

The FDA (i.e., Center for Biologics Evaluation and Research [CBER] and Center for Drug Evaluation and Research [CDER] has established advisory committees each consisting of clinical experts and one consumer advocate (not employed by the FDA) in designated drug classes and subspecialties. The committees are asked to consider data presented in NDA's and to advise as to whether there exists evidence of safety and effectiveness based upon adequate and well controlled studies. The committee may also be asked at times to review certain INDs, protocols, or important issues relating to marketed drugs/biologics.

### ***Amendment to an NDA:***

A submission to change or add information to an NDA or supplement not yet approved.

### ***Annual Reports:***

Annual Reports Reports are required to be filled by the holder of the NDA with the responsible FDA reviewing division within 60 days of the anniversary date for the NDA. Annual reports provide the FDA with a means of monitoring the drug's safety and quality. The following information is included in the Annual Report:

- Significant information affecting safety, effectiveness, or labeling
- Distribution data
- Labeling information
- Chemistry, Manufacturing, and Control changes
- Non-clinical laboratory studies
- Clinical data

- Status reports on postmarketing studies

### ***Annual Review:***

IRB's yearly review of a research project in which the board considers whether research should continue for another approval period. Under FDA regulation, IRB review of ongoing projects must be conducted at least annually.

### ***Audit:***

An examination of study related information conducted by sponsor personnel or by a regulatory group to verify compliance with study and regulatory procedures.

### ***Audit Certificate:***

A declaration of confirmation by the auditor that an audit has taken place.

### ***Backup Compound:***

Once a compound is found to be active in pharmacological screens, it is common for structural analogs to be developed. These analogs may also show activity in the screens and may be passed through the early development stages (e.g., mutagenicity, acute toxicology).

If the lead candidate should falter in a later development stage (e.g., formulation problems, toxicological concern), it may be possible to continue the program by developing one of the backup compounds.

### ***Bioavailability/Bioavailability Study:***

Bioavailability refers to the portion of an administered dose of drug that is actually available from the systemic circulation (i.e., bloodstream) to the target organ. If the drug is administered other than intravenously (e.g., orally, intramuscular injection, topically), the amount of drug available to the target organ is generally reduced due to incomplete absorption, metabolism by the liver, distribution into other tissues, etc., before entering the systemic circulation.

Bioavailability "studies" are performed to determine the extent of a drug's bioavailability.

### ***Bioequivalence Study:***

Study performed to compare the availability (in systemic circulation) of a drug substance when administered in different dosage forms. A bioequivalence study will typically compare the rate of absorption into the blood stream, the maximum level reached, the total amount of drug which reaches the blood stream, and the rate of elimination.

### ***Biologics:***

Product produced in living cells or animals (e.g., virus, blood product, toxin). Biologics used for diagnosis and treatment of human disease are subject to FDA regulation.

### ***Bioresearch Monitoring Program:***

A compliance program under which FDA inspects investigators, IRBs, and sponsors conducting clinical research to ensure its conduct according to Good Clinical Practices (GCP). This program encompasses drugs, devices, and biologics.

### ***Blinding/Masking:***

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single blinding usually refers to the subject(s) being unaware, and double blinding usually refers to the subject(s), investigator(s), monitor and, in some cases, data analyst(s) being unaware of the treatment assignment(s). Open label would mean that no one is blinded and the study treatment are known to the investigator, sponsor and subjects.

### ***Blinded Study:***

Method used to reduce bias error of data where subjects and/or study personnel do not know which subjects are being treated with investigational drug.

### ***Bulk Substance Synthesis:***

The manufacture of a drug substance in quantities sufficient to support clinical trials and later commercial sale of the drug product. The process for making these supplies generally evolves and improves over time to solve long term economic and proprietary considerations.

### ***CANDA:***

Acronym for computer assisted New Drug Application.

The provision by a drug sponsor of its entire clinical database, and perhaps animal toxicology database, in electronic computer files. The equipment needed to use these databases is generally also provided.

The availability of these databases and equipment allow the FDA to view and analyze the data in ways other than that provided in the hard copy of the submitted NDA. The CANDA is meant to supplement the NDA for more efficient and effective review by the FDA; an NDA in traditional format (i.e., hard copy) must always be submitted.

### ***Carcinogenicity Studies:***

Long term preclinical studies of at least a 2 year duration conducted in rats and mice to determine a compound's likelihood to produce malignant tumors (cancer). These studies are required for drugs intended for chronic or intermittent use consisting of continuous use for 6 months or intermittent use for at least a 6-month period to treat a recurrent disease. Due to the long duration and costs, carcinogenicity studies normally are not initiated until after the drug exhibits an indication of efficacy in Phase II trials and are usually conducted as part of the chronic (long-term) preclinical studies.

### ***Case Report Form (CRF):***

A record of clinical study observations and other information completed for each subject in a study. The data may be recorded on paper or electronically on a computer.

### ***Chronic Toxicity Studies:***

Preclinical animal studies required to be conducted for drugs intended to be used for chronic and intermittent use in large populations. Initiated after indication of efficacy in Phase II trials and conducted concurrently with Phase III trials. These studies may be coupled with the conduct of carcinogenicity studies.

These studies are conducted to determine the drug's safety profile regarding :

- Potential risks
- Potential target organ toxicities Reversibility of any observed toxicity

- No Observed Adverse (Toxic) Effect Level (NOAEL) and Maximum Tolerated Dose (MTD)

The study criteria include :

- Tests in rodent and non-rodent species
- ICH recommends a testing duration of at least 6 months which has been accepted by FDA, however FDA still recommends a 12-month study

### ***Clinical Development Plan (CDP):***

A clinical strategy outlining a study or studies to support a project plan for development of a drug.

### ***Clinical Efficacy:***

Power or capacity to produce a desired effect (i.e., appropriate pharmacological activity in a specified indication) in humans.

### ***Clinical Pharmacology:***

The properties and reactions of drugs, especially with relation to their therapeutic value, in humans. Includes the general areas of toxicology/safety, pharmacokinetics (ADME), and pharmacodynamics (reaction of drugs with living structures).

### ***Clinical Protocol:***

Document describing a clinical study and how it is to be conducted. A protocol includes the objectives of the study, the study design, a description of the test article(s) and dosage, the experimental procedure, handling of adverse reactions, how the results will be analyzed, and consent and clearance provisions.

### ***Clinical Research Associate (CRA):***

The individual responsible for carrying out on-site monitoring, data verification, and reporting on the progress of the study.

### ***Clinical Research/Development:***

The testing of a drug compound in humans primarily done to determine its safety and pharmacological effectiveness. Clinical development is done in phases which progress from very tightly controlled dosing of small number of subjects to less tightly controlled studies involving large numbers of patients.

### ***Clinical Study/Trial:***

Human studies designed to distinguish a drug's effect from other influences, for example, a spontaneous change in disease progression or in the effect of a placebo (an active substance that looks like the test drug). Such studies conducted in this country must be under an approved IND under the guidance of an institutional review board and in accord with FDA rules on human studies and informed consent of participants.

### ***CMC:***

Acronym for chemistry manufacturing, and controls section of an NDA. The documents in this section fully describe the composition, manufacture, and specifications of the drug substance and the drug product.

### ***Code of Federal Regulations (CFR):***

Document that contains FDA published regulations which can be found in 21CFR.

### ***Compassionate Use:***

Use of the drug of the investigational drug in patient for whom a beneficial effect may be present but who normally cannot qualify for enrollment in a clinical study. A special protocol must be prepared by the sponsor.

### ***Computer Validation:***

Ongoing process of evaluation and documentation of the hardware and software of a system during acquisition, implementation, and use to ensure accurate and reliable compliance with user requirements.

### ***Contract Research Organization (CRO):***

A person or an organization (commercial, academic, or other) contracted by the sponsor to assume and perform one or more of a sponsor's trial related duties and functions.

### ***Control(s):***

A well controlled study permits a comparison of subjects treated with the investigational drug and with a suitable control population, so that the effect of the investigational drug can be determined and distinguished from other influences, such as spontaneous change, placebo effects, concomitant therapy, or observer expectations. FDA regulations [21 CFR 312.126] cite five different kinds of controls that can be useful in particular circumstances:

- placebo concurrent control
- dose comparison concurrent control
- no-treatment concurrent control
- active treatment concurrent control, and
- historical control

### ***Crossover Design:***

Each subject functions as their own control in this study design; subjects are assigned to receive test and control articles in an order determined by randomizations. Subjects and investigators are blinded and there is usually a washout period between phases.

### ***Curriculum Vitae (CV):***

A formal listing of a person's academic background and training. For investigators and subinvestigators this includes a listing of medical school, residencies, fellowships, and publications.

### ***Database:***

A collection of electronic files containing the information recorded on and derived from the case report forms (CRFs).

### ***Data Management:***

The process of handling clinical study data. Data management begins with the submission of the CRF to the sponsor and includes activities regarding database creation, data entry, review, coding, data editing, data QC, archiving and reporting of the database.

### ***Data Management Personnel:***

Members primarily responsible for database creation, data validation, integration, coding, and QC, archiving and preparing data displays.

### ***Data Monitoring Committee:***

An independent committee established by the sponsor to access at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

### ***Declaration of Helsinki:***

Worldwide accepted ethical practices which govern the conduct of clinical trials. These principles define the rights of research subject participating in a study and the obligations of the investigator.

### ***Development:***

Term used to describe the program for advancing a drug compound generally from the preclinical decision to concentrate on a single compound in a research program through its approval for marketing by the FDA and other regulatory agencies.

### ***Development Candidate:***

A drug compound which has progressed sufficiently through its screening and preclinical phases to be considered for complete development through approval for marketing.

### ***Direct Access:***

Permission to examine, analyze, verify and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subject's identities and sponsor's proprietary information.

### ***Discovery Research:***

The early phases of the overall drug development process dealing with the synthesis of/search for compounds and the screening processes developed to identify "lead" compounds. The discovery phases relate to the "research" component of "research and development".

New drug development starts with an understanding of how the body functions, both normally and abnormally, at its most basic levels. The questions answered help determine a concept of how a drug might be used to prevent, cure, or treat a disease or medical condition. This provides the researcher with a target. In a series of test tube experiments called assays, compounds are added one at a time to enzymes, cell cultures, or cellular substances grown in a laboratory. This

process may require testing hundreds of compounds and will indicate ways of changing the compound's chemical structure to improve its performance.

Computers can be used to simulate a chemical compound and design chemical structures that might work. Enzymes attach to the correct site on a cell's membrane, which causes the disease. A computer can show scientists what the receptor site looks like and how one might tailor a compound to block an enzyme from attaching there.

Another approach involves testing compounds made naturally by microscopic organisms. Candidates include fungi, viruses and molds, such as those that led to penicillin and other antibiotics. Scientists grow the microorganisms in what is known as a "fermentation broth," with one type of organism per broth.

### ***Dissolution:***

**A laboratory test to measure of the rate at which a formulated drug product breaks down in simulated gastrointestinal fluids as measured by the release the active drug over a period of time. This information can be used as a measure to estimate levels of the drug that can be found in the blood.**

### ***Documentation:***

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records; and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

### ***Dosage Form:***

The "delivery system" for a drug product, e.g., tablet, capsule, I.V. solution, topical cream.

### ***Dose:***

The amount of drug administered to a patient or test subject.

### ***Double Blind:***

Study design in which neither research team nor subject know whether they are receiving test medication or control.

### ***Drug:***

(Food, Drug, & Cosmetic Act) (1) a substance recognized by an official pharmacopoeia or formulary, (2) a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, (3) a substance other than food intended to affect the structure or function of the body, (4) a substance intended for use as a component of a medicine but not a device or a component, part, or accessory of a device.

### ***Drug Development Process:***

The entirety of the activities and decision making which must be completed in a program meant to discover a new active substance and progress it through approval by the FDA for marketing as a new drug product.

### ***Drug Product:***

A finished dosage form (e.g., tablet, capsule, solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

***Drug Substance:***

An active ingredient in a drug product that is intended to furnish pharmacological activity or other direct effect in the diagnosis, care, mitigation, treatment or prevention of disease or to affect the structure or any function of the human body.

***Effectiveness:***

The desired measure of a drug's influence on a disease condition. Effectiveness must be proven by substantial evidence consisting of adequate and well controlled investigations, including human studies by qualified experts, that prove the drug will have the effect claimed in its labeling.

***Efficacy:***

Power or capacity to produce a desired effect (e.g., appropriate pharmacological activity in a specified indication).

***ELA (Establishment License Application):***

Document(s) submitted to the Center for Biologics Evaluation and Research (CBER) to obtain an Establishment License.

***Emergency Research:***

Life-threatening situation where another marketed drug is available and Investigator cannot obtain informed consent from the subject or their legal guardian, investigator may administer investigational drug to a subject as part of an IRB approved study. The subject and/or legal guardian must be informed following this investigational use of the drug and informed consent obtained.

***Establishment Inspection Report (EIR):***

Report prepared by FDA inspector as a result of a field inspection. EIRs are classified as NAI, VAI, and OAI (see appropriate sections of this glossary for definitions).

***Essential Documents:***

Documents "which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced." (ICH Guideline for GCP 8.1) Examples: investigator's brochure, protocol, informed consent form, monitoring reports, CRFs, source documents, IRB/ERC approvals.

***Ethics Review Committee (ERC):***

Term used to describe an non-U.S. independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and nonmedical/nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing

favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations, and regulatory requirements pertaining to Independent Ethics Review Committees may differ among countries, but should allow the Independent Ethics Review Committee to act in agreement with GCP as described in this guideline.

### ***Exclusion Criteria:***

Items specified in a study protocol prohibiting subject participation in a clinical trial (e.g., medical restrictions, behavioral characteristics). Exclusion and inclusion criteria define the study population.

### ***FDA 1571:***

The cover sheet for a Investigational New Drug Application (IND) submitted to FDA which reports the phase of a proposed study, outlines the allocation of responsibility for the study, and documents the sponsor's agreement to follow applicable regulations.

### ***FDA 1572:***

Signed agreement from the investigator required for studies conducted under U.S. IND which indicates that the requirements for conducting the study, including the investigator's obligations are understood by the investigator and that the qualifications to conduct the trial are met. Receipt of the FDA 1572 by the sponsor is required prior to shipment of any investigational drugs to investigator.

### ***FDA 482 Form:***

Notice of inspection presented to investigator/sponsor/contract research organization by an FDA inspector to notify them of FDA's intent to conduct an inspection.

### ***FDA 483 Form:***

Form issued by FDA inspector to investigator/sponsor/contract research organization notifying them of any regulatory violations observed during FDA audit.

### ***Clinical Study Report (CSR):***

The report that describes the results of a clinical study in which the clinical and statistical descriptions, presentations, and analyses are integrated into a single report, incorporating tables and figures into the main text of the report, or at the end of the text, and with appendices containing the protocol/protocol amendments, investigator information, related publications, patient data listings, and technical statistical details such as derivations, computations, analyses, and computer output, etc."

### ***End of Phase II Meeting:***

The primary focus of "end of Phase 2" meetings is to determine whether it is safe to begin Phase 3 testing. This is also the time to plan protocols for Phase 3 human studies and to discuss and identify any additional information that may be required to support the submission of a new drug

application. It is also intended to establish an agreement between the Agency and the sponsor of the overall plan for Phase 3 and the objectives and design of particular studies. These meetings avoid unnecessary expenditures of time and money because data requirements have been clarified.

One month prior to the "end of the Phase 2" meeting, the sponsor should submit the background information and protocols for Phase 3 studies. This information should include data supporting the claim of the new drug product, chemistry data, animal data and proposed additional animal data, results of Phase 1 and 2 studies, statistical methods being used, specific protocols for Phase 3 studies, as well as a copy of the proposed labeling for a drug, if available. This summary provides the review team with information needed to prepare for a productive meeting.

### ***Food and Drug Administration (FDA):***

The regulatory authority in the United States which oversees the activities of the pharmaceutical industry. The FDA is responsible for approving drugs by ensuring that drugs marketed in the US have a greater benefit than risk when used according to manufacturer's directions.

### ***For Cause Inspection:***

FDA inspection normally conducted when agency suspects fabrication of data or violation of informed consent regulations. May occur following reports of serious violations found in a routine inspection or may follow an investigator/sponsor report to FDA of problems encountered. A report of practices received from an investigator's patients, colleagues, or employees may also instigate an inspection.

### ***Formulation Development:***

Production of an appropriate pharmaceutical dosage form (drug product and/or drug delivery system) along with the process for its manufacture, the documentation covering its manufacture and the specifications and test methods relevant to identity, strength, dose uniformity, quality, stability bioavailability along with those properties that permit its manufacture on high speed machinery, shipment in commercial channels and storage. A large number of formulations of the same drug may be provided for both clinical and pharmaceutical study/use.

### ***GCP (Good Clinical Practices\*):***

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

### ***GLP (Good Laboratory Practices\*):***

Worldwide regulations governing the conduct of non clinical animal studies from which data will be used to support applications for research (e.g., IND) or marketing (e.g., NDA) permits.

### ***GMP (Good Manufacturing Practices\*):***

Worldwide regulations governing the manufacture of human and animal drugs. GMP regulations apply to the manufacture of drug supplies used in the conduct of clinical research studies as well as marketed drugs.

\*All of these regulations intend to establish minimum standards for: safety; validity and accuracy of data; consistency between research and manufacturing performed in different facilities and in

different countries. These standards allow regulatory oversight, require self inspection and reporting, and address a link to the product license. The focus of the regulations: (1) defines responsibilities of management, assignment of individual and personal qualifications; (2) assures that facilities and equipment are appropriate for use; tested, maintained and repaired; and that appropriate documentation is kept; (3) requires written procedures (SOPs), protocols, in-house records and record retention.

### ***ICH Guidelines:***

A set of guidelines developed by the International Conference on Harmonization made up of industry and government representatives from the U.S., Japan and Europe designed to govern the worldwide development of drugs in conformance with accepted practices and ensure the mutual acceptance of the data.

### ***Inclusion Criteria:***

Essential characteristics the subject must have to be included in a clinical trial.

### ***In vivo Pharmacology:***

The study of the origin, native chemistry, effects and uses of drugs following administration to living organisms: non clinical in animals; clinical in humans (vs. ex vivo - "living" parts of organisms removed from the body of the organism).

### ***IND/Investigational New Drug Application (Claimed Notice of Investigational Exemption):***

(Code of Federal Regulations, Title 21, Part 312) Documentation that must be submitted to the FDA before a new drug (or biologic) can be shipped interstate for human testing. (In practical terms, all major companies file an IND, and await the 30-day review period before first administration of a compound to man.) This includes all appropriate evidence that clinical investigations can be performed with reasonable safety to the subject or patient (first animal safety test, pharmacology, manufacturing procedures, and proposed first protocol). Following initial filing, the IND becomes a "central file" for information on the drug/biologic (new formulations and/or indications on the compound may require an additional separate IND to be filed).

All relevant subsequent information (amendments) should be forwarded, e.g., final study reports, serious adverse experience reports, new protocols (both clinical and non clinical) and a yearly progress report summarizing the last year's information and proposed plan for the future year.

### ***Indication:***

Disease or condition for which a drug has been approved by the FDA or another regulatory agency.

### ***Informed Consent:***

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

### ***Informed Consent Form:***

A document approved by the Institutional Review Board/ Ethics Review Committee (IRB/ERC) which describes to a potential subject the aims, methods, anticipated benefits, and potential hazards of an investigational study in a language he/she understands.

### ***Institutional Review Board (IRB):***

An independent body as defined by FDA regulations 21CFR part 56, which is constituted of medical, scientific, and nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Each IRB must contain at least five members of varying backgrounds (both scientific and nonscientific, e.g., law, religion, ethics). The IRBs are required to convene in order to review studies and must conduct continuing review on at least an annual basis.

### ***Investigator:***

An individual who is qualified by training and experience (e.g., physician, dentist, clinical psychologist) to conduct a clinical study. He/she assumes direct responsibility for the welfare of subjects under his/her care, including the obligation to enroll subjects, to report adverse events, and to discontinue their treatment if there is real or anticipated danger.

### ***Investigator's Brochure (IB):***

A document containing information about the investigational drug including a description of the drug formulation, a summary of toxicological and pharmacological effects of the drug, a summary of the pharmacokinetics of the drug, a summary of safety and effectiveness, and a description of possible risks and side effects. The IB must be updated whenever there is relevant new information about the drug.

### ***Kefauver-Harris Amendment:***

1962 Congressional act requiring comparison trials to show drug efficacy; led to law requiring blinded controlled trials in clinical evaluation.

### ***Labeling:***

Description of drug and summary of use, safety, and effectiveness. New drug labeling must be approved by FDA at the time of NDA review.

### ***Lead/Lead Compound:***

A compound with activity of sufficient interest to warrant a request for resynthesis is usually considered a lead compound (drug metabolism studies; preliminary animal safety studies; adequate analytical chemistry and pharmaceutical profile). Procedures vary among companies. Normally, the compound will be the first in a "family" of similar compounds that a company will develop to cover a specific population/indication.

### ***Life threatening adverse experience:***

Any adverse experience that places the patient, in the view of the investigator, at immediate risk of death from the adverse experience as it occurred, i.e., it does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

### ***Line Extension:***

Marketing term generally used to denote additional dosage forms of a particular drug compound. The extension (new product) may be a different dose strength of an approved dosage form (e.g., tablet) or a new dosage form *per se* (e.g., a sustained release tablet vs. an immediate release tablet).

### ***Long-Term Preclinical Animal Testing***

Long-term testing in animals ranges in duration from a few weeks to several years. Some animal testing continues after human tests begin to learn whether long-term use of a drug may cause cancer or birth defects. Much of this information is submitted to FDA when a sponsor requests to proceed with human clinical trials. The FDA reviews the preclinical research data and then makes a decision as to whether to allow the clinical trials to proceed (see Clinical Development ).

### ***MAA (Marketing Authorization Application):***

An MAA (Marketing Authorization Application) is a general term for registration documents seeking approval to market a drug product. In Europe, an MAA would imply a document used for multi-national submission as opposed to seeking approval in only a specific country.

### ***Marketing Support Trials:***

(See also Phase IV studies) Studies to assess not only safety and efficacy on much larger patient populations, but also quality-of-life impact and cost effectiveness and drug interaction. Marketing support studies and research overhead, result in publications and address medical needs.

### ***Medical Monitor:***

Physician representing the sponsor who has medical authority for clinical trial.

### ***Metabolism:***

The investigation of the physiological disposition and biotransformation of the drug/biologic. (Non clinical -- study in animals; clinical -- study in humans.) The metabolism of many drugs is the major determinant of the intensity and duration of their pharmacological and adverse side effects. Information regarding the routes and rates of metabolism is therefore helpful in designing optional drug candidates.

### ***Monitoring:***

The act of overseeing a clinical trial, and of ensuring that it is conducted, documented, and reported in accordance with the protocol, standard operating procedures (SOP's), GCP, and the applicable regulatory requirement(s).

### ***Monitoring Visit:***

A visit to a study site to review the progress of a clinical study and to ensure protocol adherence, accuracy of data, safety of subjects, and compliance with regulatory requirements and good clinical practice guidelines.

***Mutagenicity / Genotoxicity Studies:***

Preclinical *in-vitro* and *in-vivo* studies conducted to aid in the interpretation of observed teratogenic and carcinogenic effects the new drug may cause. The studies determine if the new drug may potentially cause any gene mutations, chromosomal damage and/or primary DNA damage.

***New Drug:***

A drug first investigated or proposed for marketing after 1938 (when the Federal Food, Drug, and Cosmetic Act was passed), that is, the drug was not generally recognized as safe and effective before that date.

***NCE (New Chemical Entity):***

A compound that can be patented, which has not previously been approved.

***NDA (New Drug Application):***

The marketing application in the US for a new drug, containing all pre-clinical, clinical, and manufacturing data, plus the proposed labeling of the study drug.

***No Action Indicated (NAI):***

Classification of an Establishment Inspection Report (EIR) which says the establishment is in compliance. A letter may be issued at the discretion of the FDA. No response is necessary - routine reinspection.

***Official Action Indication (OAI):***

Classification of an Establishment Inspection Report (EIR) which says objectionable conditions are such that regulatory and/or administrative sanctions will be recommended due to the impact on study integrity.

***Open Label:***

Study design in which drug given to subjects is known to both investigator and subjects. No placebo used.

***Over-the-Counter Drugs (OTC):***

Drugs that may be purchased without a prescription.

***Package Insert (PI):***

A product information sheet which contains a succinct summary of the whole development process. It distills the chemical, pharmacological, toxicological, metabolic, and clinical data into relatively few paragraphs. Negotiating the wording of this document can be one of the major events in the entire approval process.

***Parallel Track Mechanism:***

A U.S. Public Health Service policy that makes promising investigational drugs for AIDS and other HIV related diseases more widely available under "parallel track" protocols while the controlled clinical trials essential to establish the safety and effectiveness of new drugs are carried out. The system established by this policy is designed to make the drugs more widely available to patients with these illnesses who have no therapeutic alternatives and who cannot participate in the controlled clinical trials.

### ***PDUFA:***

Acronym for the Prescription Drug User Fee Act

### ***Periodic Adverse Experience Reports:***

These are periodic reports of adverse experiences that must be submitted to FDA quarterly for the first three years following a drug's approval then yearly thereafter. All quarterly reports must be submitted within 30 days and yearly reports within 60 days of the NDA approval date. The information to be included:

- A copy of each FDA 3500A (MedWatch) for each AE not reported as a 15-Day Report.
- A narrative summary and analysis of the information in the 15-day Reports submitted during the reporting period.
- A narrative discussion of any actions taken since the last report due to AEs ( e.g., labeling changes, clinical studies conducted, etc.).

### ***Pharmacodynamics:***

Action of a drug on the body's various receptors or major physiological systems. To determine the underlying characteristics of a drug is its interactions with its receptors.

- Does the drug bind to the specific receptors for which it was designed and with what affinity is its binding selective?
- What effects does its binding have on the CNS, GI tract, hemodynamics or other cardiovascular parameters?
- What is the dose response relationship?
- What is the duration of action and mechanism of action? hat is the dose responWhat is the duration of action and mechanism of action?

### ***Pharmacokinetics:***

Studies that provide information on the rate and extent of absorption, distribution, metabolism, and excretion of a compound, as well as its localization in tissues (ADME).

### ***Pharmacology:***

The science that deals with the effect of drugs on living organisms.

### ***Phase I Clinical Trials:***

The initial introduction of a new drug or biologic into humans at a stage when only animal and *in vitro* data are available. These studies are often referred to as "clinical pharmacology". These studies are primarily designed to determine the metabolism, pharmacological action and safety of the drug in humans. More specifically, Phase I studies help to determine a safe dosage range of the drug in humans, provides information of drug absorption, distribution, metabolism, and elimination (ADME), and possibly early evidence of effectiveness. Review of data from Phase I

is essential prior to proceeding to Phase II clinical development. The study characteristics for Phase I trials are:

- normal volunteers, patients occasionally
- 50-100 subjects
- close monitoring
- The initial types of Phase I studies include:
  - single dose
  - ascending dose tolerance
  - multiple dose
  - seven (7) day ascending dose tolerance
  - 28 day tolerance of highest dose

Later development studies include trials conducted during Phase II / III are conducted to determine interactions with other drugs, bioequivalence and testing special populations (e.g., renal impairment, elderly, etc.).

### ***Phase II Clinical Trials:***

The first time a drug is used in humans to prevent or treat the disease for which it is intended. Close clinical monitoring is conducted on a relatively small number of subjects to determine the drug's short term efficacy and its potential risks (safety). These trials are normally divided into two segments, Phase IIa and Phase IIb.

The characteristics for Phase II development include:

- Small, controlled studies
- Limited populations - 100-200 subjects

During Phase II it is essential to correlate blood levels with pharmacologic effects (i.e., pharmacodynamics and adverse events). As the results of Phase II trials, drugs with genuine potential are differentiated from those which are ineffective and/or not well tolerated.

### ***Phase IIa:***

First clinical studies in a small number of patients to demonstrate safety and first signs of efficacy.

### ***Phase IIb:***

These are the initial dose ranging efficacy trials. They are more extensive than Phase IIa patient studies and are used to establish dose and overall efficacy/safety properties. These studies also establish the initial benefits to risk ratio. The results of these trials are used to determine the study design and dosing for Phase III trials.

### ***Phase III:***

Expanded controlled and uncontrolled clinical trials intended to gather additional evidence of efficacy for specific indications being studied and to better understand safety and drug related adverse effects. Phase III trials are usually large multi-center trials which collect substantial safety experience efficacy information and include the pivotal trials which serve the basis for drug approval. Phase III trials may also include specialized studies needed for labeling (e.g.,

pediatric or elderly, comparative agents). Several hundred to several thousand patients may be included in the Phase III trials.

These studies are specifically designed to:

- verify effectiveness
- monitor effects from long term use
- establish labeling requirements
- determine overall risk/benefit

### ***Phase IIIb:***

Studies conducted after the drug has been approved for marketing. The purposes of these studies include differentiation from other treatments, exploring use in additional patient populations, seeking new indications for the study, or exploring AEs.

### ***Phase IV:***

These are marketing oriented trials which may extend the recommended duration of treatment or they may be primarily instructive in nature to help familiarize a larger number of practitioners with the drug's efficacy and side effects (seeding studies).

### ***Pivotal Studies / Trials:***

These are the adequate and well controlled Phase III trials which provide the substantial evidence of effectiveness and safety upon which the drug is approved.

Adequate and well controlled trials possess the following characteristics:

- blinding
- randomization
- controls
- sufficient size

### ***Post-marketing Surveillance:***

Clinical studies carried out by a company following market introduction to evaluate a new drug under conditions of actual medical practice. The studies may be initiated by the manufacturer to clarify why and how a new drug is used and determine whether the adverse experience profile established in controlled trials reflects the true properties of the drug. Such studies may also be required by a regulatory health authority as a condition for approval.

### ***Preclinical Development:***

This refers to the work performed on a potential new drug from the time it passes a company's first set of acceptance criteria until the first administration of the substance to humans. The phase typically ends upon submission of a data package to a regulatory health authority (see IND). The term may also be used to refer to drug development work other than clinical trials which takes place during the clinical development phases, although the term non clinical is more accurate.

### ***Preclinical Animal Studies:***

Studies that test a drug on animals and other non human test systems. Data about a drug's activities and effects in animals help establish boundaries for safe use of the drug in subsequent human testing (clinical studies). Also, because animals have a much shorter life span than

humans, valuable information can be gained about a drug's possible toxic effects over an animal's life cycle and on offspring.

### ***Pre-IND Meeting***

Prior to clinical studies, the sponsor needs evidence that the compound is biologically active, and both the sponsor and the FDA need data showing that the drug is reasonably safe for initial administration to humans. Under FDA requirements, the sponsor usually must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies.

Pre-IND meetings are conducted with the appropriate review division that would review the drug marketing application and these meetings are typically requested by the sponsor of a drug.

Meetings at such an early stage in the process are useful opportunities for open discussion about testing phases, data requirements, and any scientific issues that may need to be resolved prior to IND submission. At these meetings, the sponsor and FDA discuss and agree upon the design of the animal studies needed to initiate human testing. (see *CFR 312.47, and CFR 312.82*).

### ***Pre-NDA Meeting:***

The purpose of a Pre-NDA meeting is to discuss the presentation of data (both paper and electronic) in support of the application. The information provided at the meeting by the sponsor includes:

- A summary of clinical studies to be submitted in the NDA,
- The proposed format and organization of the submission, including methods for presenting the data; and
- Other information needed to be discussed.

This meeting is designed to:

- Uncover any major unresolved problems or issues,
- Identify studies the sponsor is relying on as adequate and well controlled in establishing the effectiveness of the drug,
- Help the reviewers to become acquainted with the general information to be submitted, and
- Review the presentation of the data in the NDA to facilitate its review.

Once the NDA is filed, an additional meeting may also occur 90 days after the initial NDA submission in order to discuss issues uncovered in the initial review.

### ***Process Development:***

The component of drug development concerned with systems, methods, and procedures for producing a drug substance or drug product. It evolves in parallel with the overall drug development process beginning with supply of toxicology and early clinical material and proceeds through an up-scaling program to the point where it is capable of meeting commercial demands in terms of quality and quantity.

### ***Product License Application (PLA):***

A Product License Application is a term which can be applied to the body of information which is submitted to a regulatory authority as a basis for determining whether a new biologic should be approved for marketing.

In the US the term refers specifically to the collection of information submitted to the FDA for a new biologic product in order to obtain a "product license". A "product license" must be requested and issued simultaneously with the "establishment license".

The combination of the establishment and product licenses for a biologic is analogous to a New Drug Application (NDA) for "non biologic" drug product.

### ***Protocol Amendment:***

A written description of a change(s) to or formal clarification of a clinical protocol.

### ***Quality Assurance:***

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s).

### ***Randomization:***

The process of randomly assigning patients to one of at least two treatment groups with pre-determined probability of assignment to each treatment group.

### ***Raw Data:***

Researcher's records of patients, such as patient charts, hospital records, x-rays, and attending physician's notes. These records may or may not accompany an NDA, but must be kept in the researcher's file. FDA may request their submission or may audit them at the researcher's office.

### ***Reproductive/Teratology Studies:***

These are special preclinical animal toxicological studies aimed at assessing the potential risk of a drug on reproduction and early development. These studies are required for drugs intended or have the potential to be used on women of childbearing potential. These studies normally are initiated prior to or early during clinical testing and continue throughout the clinical development of the compound with the final tests completed just prior to filing.

Reproductive/Teratology studies are typically conducted into three phases or segments:

- **Segment I - Fertility and General Reproductive Performance**
  - Study of fertility and general reproductive performance, e.g., mating behavior, gonadal function, conception, and early gestation
  - Required to initiate short term trials in females
  - Species studied include male and female rats
- **Segment II - Teratology Study**
  - Measure the embryo toxic (embryo lethality) and/or teratogenic (external visceral and skeletal defects) effects caused by administration of new drug to pregnant females during organogenesis
  - Two species are studied, the rat and rabbit (mouse and primate are also studied if indicated)

- **Segment III - Perinatal and Postnatal Study**
  - Study of perinatal and postnatal effects, e.g., on late stage fetal development, labor, delivery, lactation, viability, and growth of the newborn
  - Assessments include observations of labor; deliver; lactation; viability, growth, development, and weaning of newborn
  - Species studied include the rat (mouse or primate if indicated)

### ***Regulatory Authorities:***

Bodies having the power to regulate. In the ICH GCP guideline the expression *Regulatory Authorities* includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

### ***Research:***

The process of scientific investigation or inquiry; in this usage, it involves the work carried out to discover and bring new pharmaceutical products to the market. It is often used in combination with many terms to distinguish among various types of research such as basic research, discovery research, applied research, preclinical research, clinical research, etc.

### ***Risk:***

A factor, element, or course of action involving an uncertain, potentially negative outcome. In drug development, it can have several usages such as the degree of uncertainty associated with a new project which may influence the degree to which resources should be committed. This is often expressed relative to the potential reward for a new project as a factor in balancing a development portfolio.

Risk may also refer to the safety profile of a drug which can be evaluated as a stand alone characteristic or relative to its efficacy profile as an expression of the "benefit/risk assessment". The latter may also influence internal decision making as well as the attitudes that regulatory health authorities will have concerning approval of a new product.

### ***Risk-Benefit Assessment:***

Process in which the relative risks and benefits of clinical trial participation are identified and compared. This process is central to the IRB approval process and also in the subject's evaluation of the project in the informed consent form.

### ***Routine Inspection:***

Part of the Bioresearch Monitoring Program established by the FDA to oversee conduct of clinical investigators, sponsors, biopharmaceutical laboratories, institutional review boards, and toxicology laboratories. Inspections non directed, non casual.

### ***Safety/Safety Assessment:***

Safety is the property of a drug related to its potential to cause injury (also see Adverse Experience). Safety assessment is the component of drug development research concerned with identifying and quantifying the degree of risk of causing injury associated with a drug. It incorporates studies carried out preclinically and clinically as well as monitoring for adverse effects post-approval during marketing.

The safety of drugs is a relative property in several ways. Drugs are often compared with each other with or without regard to their positive attributes to conclude that one is "safer" than the other. The relative safety of a drug can be dependent on the disease or condition for which it is used. For example, two agents with identical adverse experience profiles would be regarded very differently if one is used for AIDS and the other for rhinitis. The safety profile of a drug may depend to a great extent on whether it was developed only on the basis of controlled clinical trials or alternately has evolved over many years of market experience.

### ***Safety Assessment Candidate:***

A substance which has demonstrated activity in a relevant assay or model without adverse properties which rule it out as a potential drug. In some companies this represents the point at which it enters formal development, while other companies may wait for additional data. The substance will then be studied in a range of preclinical toxicology assays to generate a profile which is used as a factor in the decision as to whether to proceed towards an IND and administration to humans.

### ***Safety Reports (IND Safety Reports):***

Expedited of significant safety information for all AEs that are determined to be: serious; unexpected; and associated with the use of an investigational drug (related). These reports must be submitted to regulatory authorities and all clinical investigators within 15 calendar days (ICH). For those AEs that result in death or if the AE is life threatening, a telephone/fax report must also be made to the regulatory authority within 7 calendar days (ICH).

### ***Safety Update Reports:***

Reports that an NDA sponsor must submit to FDA about any new safety information that may affect the use for which the drug will be approved, or draft labeling statements about contraindications, warnings, precautions, and adverse reactions. Safety update reports are required every four months after the application is submitted for the first 3 years after the applicant receives an approvable letter, and annually thereafter.

### ***Screen/Screening:***

Screening is the process by which substances are evaluated in a battery of tests or assays (screens) designed to detect a specific biological property or activity. It can be conducted on a random basis in which substances are tested without any pre-selection criteria or on a targeted basis in which information on a substance with known activity and structure is used as a basis for selecting other similar substances on which to run the battery of tests.

### ***Serious adverse experience:***

Any adverse experience occurring at any dose that results in any of the following outcomes: death, a life threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one. Events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### ***Short -term Preclinical Animal Studies***

Preclinical animal studies required to support an IND to initiate clinical testing. These studies consist of the pharmacology testing sufficient to develop pharmacological profile of the drug and the toxicity studies needed to establish a safety profile. These studies normally include:

- Acute toxicity testing in several species using route of administration for clinical use
- Subacute or subchronic toxicity studies ranging from 2 weeks to 3 months
- Initiation of reproduction study (Segment I)

### ***Single Blind:***

Study design in which investigator is aware of the identity of the drug received by the subject, but the subject is not.

### ***Source Documents:***

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

### ***Sponsor:***

A company or individual which plans and initiates clinical drug studies for new products.

### ***Sponsor- Investigator:***

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

### ***Stability:***

The stability of a drug/biologic substance or drug/biologic product is its resistance to change in its physical/chemical properties.

Testing of the attribute under normal and stress conditions evaluates and supports the packaging systems used, storage requirements, and the expiration dating assigned. The testing verifies that characteristics present at initial production or manufacture will remain within an established set of specifications for an appropriate length of time (shelf life).

### ***Standard Operating Procedure (SOPs):***

Written instructions describing operations to be performed and methods employed.

### ***Study Coordinator:***

Assistant to the primary investigator in a clinical study.

### ***Subacute / Subchronic Toxicity Testing:***

Preclinical animal studies conducted to observe the new drugs toxic and pathological effects over a longer period of time to support preliminary short term clinical trials (Phase I).

Study criteria :

- Studies range in length for 14 days to more than 90 days (normally not less than 28 days). The duration of the study is dependent on the proposed duration of clinical use and should exceed the duration of use in the clinical study.
- Daily administration by same route to be used in clinical studies to determine the No Observed Adverse (Toxic) Level (NOAEL)
- One rodent (rat) and one non rodent species usually a dog but a monkey is occasionally used

### ***Subject:***

Human participant in a clinical trial.

### ***Subinvestigator:***

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial related procedures and/or to make important trial related decisions (e.g., associates, residents, research fellows).

### ***Supplemental NDA (sNDA):***

Documentation submitted to FDA on a drug substance or product which is already the subject of an approved NDA. Supplements may be submitted for a variety of reasons such as labeling changes, a new or expanded clinical indication, or a new dosage form presentation.

### ***Surrogate Endpoint (Marker):***

A laboratory finding or physical sign that may not, in itself, be a direct measurement of how a patient feels, functions or survives, but nevertheless is considered likely to predict therapeutic benefit. An example would be CD4 cell counts, used to measure the strength of the immune system.

### ***Toxicology:***

The study of the nature and effects of poisonous materials. In drug development it refers to the battery of studies conducted in animals or *in vitro* test systems used to predict potential adverse experiences in humans, often at doses in excess of the intended clinical dose. Certain studies are conducted prior to first administration in humans; others are conducted during clinical development to evaluate dosing regimens or durations (e.g., lifetime carcinogenicity studies) which cannot be performed clinically.

Toxicology studies are often characterized by the duration of administration of specific targets as listed below:

- Acute: Single dose
- Subacute /subchronic: 1 week to 3 months
- Chronic: 6-12 months
- Mutagenicity/gene tox: Short term tests (*in vitro* or *in vivo* which may predict carcinogenic potential.

### ***Treatment IND:***

A mechanism that allows promising investigational drugs to be used in "expanded access" protocols, relatively unrestricted studies in which the intent is both to learn more about the drugs, especially their safety, and to provide treatment for people with immediately life threatening or otherwise serious diseases for which there is no real alternative. But these expanded access protocols also require researchers to formally investigate the drugs in well controlled studies and to supply some evidence that the drugs are likely to be helpful. The drugs cannot expose patients to unreasonable risk.

### ***Unexpected adverse experience:***

Any adverse drug experience that is not listed in the current labeling or Investigator's Brochure for the drug product. This includes events they may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

### ***User Fees:***

Charges based on a "Fee Schedule" to drug firms for certain NDAs, drug products, and manufacturing establishments as prescribed by the Prescription Drug User Fee Act (PDUFA). FDA uses these fees to hire more application reviewers and to accelerate reviews through the use of computer technology.

### ***Voluntary Action Indicated (VAI):***

Classification of an Establishment Inspection Report (EIR) which indicates that objectionable condition or practice which may or may not have been corrected during the inspection and the conditions have had a minimal effect on the integrity of the study. A letter may issue routine reinspection.

### ***Waxman-Hatch Act:***

1984 Act of Congress that extends patent exclusivity in marketing a drug for the same number of years that the regulatory process required (3-4 years). Also defined bioequivalence of some generics and eliminated many obstacles to generic product introduction in the market.

### ***Well Controlled Studies:***

Clinical studies that normally contain *blinding*; have *controls*; and are *randomized*.