1
Introduction and New Drug Development Process

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1.1 Introduction

The fundamental objective of drug development is to find a dose, or dose range, of a drug candidate that is both efficacious (for improving or curing the intended disease condition) and safe (with acceptable risk of adverse effects). If such a dose range cannot be identified, the candidate would not be a medically useful or commercially viable pharmaceutical product, nor should it be approved by regulatory agencies.

Each pharmacological agent (drug candidate) will typically have many effects, both desired (such as blood pressure reduction) and undesired (adverse effects, such as dizziness or nausea). Generally, the magnitude of a pharmacological effect increase monotonically with increased dose, eventually reaching a plateau level where further increases have little additional effect. Of course, for serious adverse effects, we will not be able to ethically observe this full dose range, at least in humans. Figure 1.1 illustrates a monotonic dose–response relationship, which could be for either a beneficial or adverse safety effect. Note that some types of pharmacological response exhibit a "U-shaped" (or "inverted U-shaped") dose–response pattern, but these are relatively rare, at least over the dose range likely to be of therapeutic value.

Figure 1.1 distinguishes between individual dose–response relationships—the three steeper curves representing three different individuals—and the single, flatter population average dose–response relationship. When discussing "dose–response" in drug development, it is generally implied the population average type of dose–response.

For a therapeutically useful drug, the "safe and efficacious" dose range will be on the low end of the safety dose–response curve and towards the higher end for beneficial effect. The concept of "efficacious dose range" and "safe dose range" is illustrated in Figure 1.2 and will be clarified in the following paragraphs.

Based on these dose–response curves, the maximum effective dose (MaxED) and the maximally tolerated dose (MTD) can be defined: MaxED is the dose above which there is no clinically significant increase in pharmacological effect or

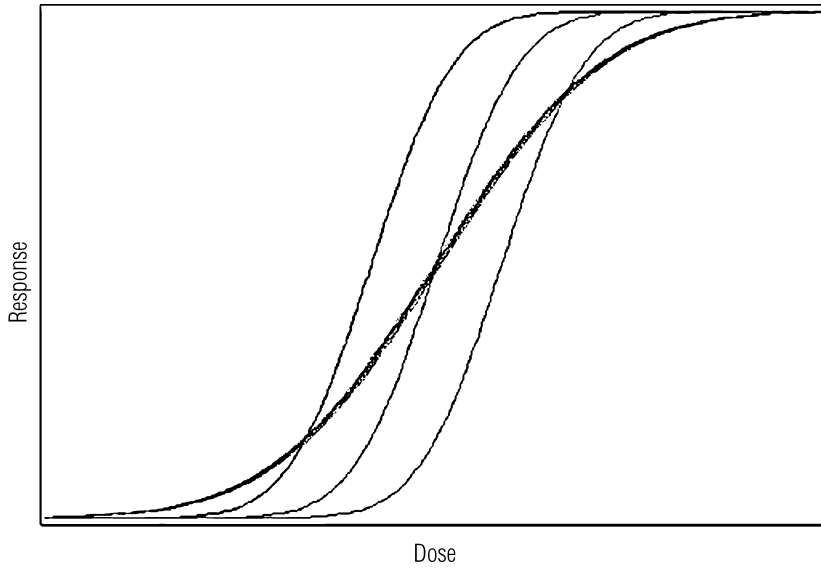

Figure 1.1. Individual and average dose–response curves.

efficacy, and MTD is the maximal dose acceptably tolerated by a particular patient population. Another dose parameter of interest is the minimum effective dose (MinED). Ruberg (1995) defines the MinED as "the lowest dose producing a clinically important response that can be declared statistically, significantly different from the placebo response".

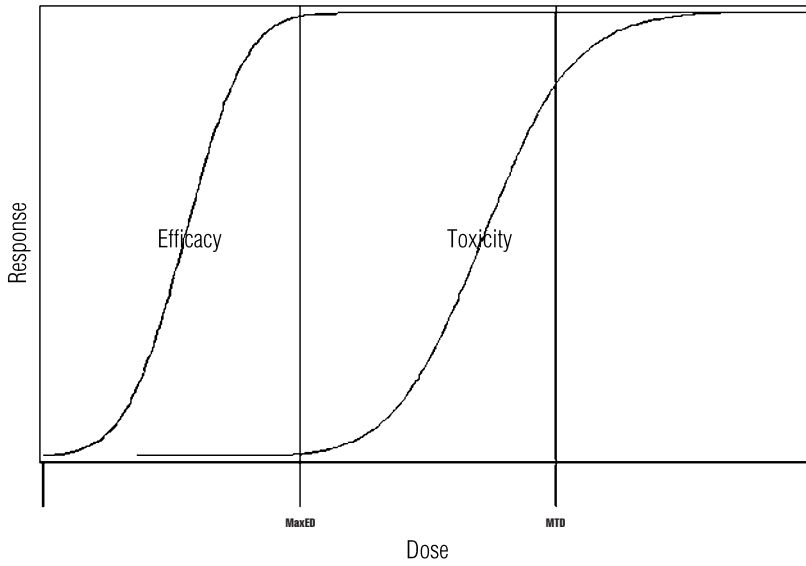

Figure 1.2. Dose–response for efficacy and toxicity.

In certain drugs, the efficacy and the toxicity curves are widely separated. When this is the case, there is a wide range of doses for patients to take; i.e., as long as a patient receives a dose between MaxED and MTD, the patient can benefit from the efficacy, and at the same time, mitigate toxicities from the drug. However, for other drugs, the two curves may be very close to each other. Under this situation, physicians have to dose patients very carefully so that while benefiting from the efficacy, patients do not have to be exposed to potential toxicity from the drug. The area between the efficacy and the toxicity curves is known as the "therapeutic window". One way to measure the therapeutic window is to use a "therapeutic index (TI)". TI is considered as the ratio of MTD over an effective dose (e.g., MaxED). Clearly, a drug with a wide therapeutic window (or a high TI) tends to be preferred by both physicians and patients. If a drug has a narrow therapeutic window, then the drug will need to be developed carefully, and physicians will prescribe the drug with caution.

It is also of interest to distinguish between the maximum effect achievable (height of the plateau) and potency (location of the response curve on dose scale). Figure 1.3 illustrates these concepts. Drugs operating by a similar mechanism of action often have (approximately) similar dose–response shapes, but will differ in potency (the amount of drug needed to achieve the same effect), e.g., Drugs A and B in Figure 1.3. Here Drug A is more potent than B because it takes less dose of A to reach the same level of response as that of B. A drug operating by a different mechanism might be able to achieve higher (or lower) efficacy—e.g., Drug C.

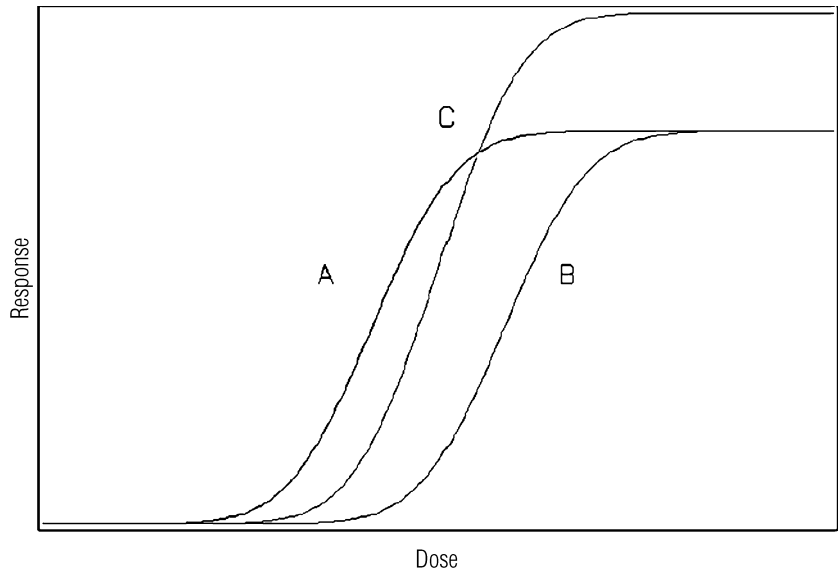

Figure 1.3. High potency drug and high efficacy drug.

The process of drug development—involving literally thousands of experiments in animals, healthy human subjects, and patients with the target disease—focuses

on achieving progressively refined knowledge of the dose–response relationships for important safety and efficacy effects. Prior to human trials, extensive in vitro (outside of a living organism) and in vivo (within a living organism) experiments are conducted with the drug candidate to identify how the various effects depend upon dose (or other measures of exposure such as its concentration in the body).

Dose–response relationship for a new drug is studied both in human and in animal experiments. Human studies are referred as clinical trials, and animal studies are generally part of nonclinical studies. In either case, experiment design and data analysis are critical components for a study. Statistical methods can be applied to help with design and analysis for both nonclinical and clinical studies. Evidences of drug efficacy and drug safety in human subjects are mainly established on the findings from randomized double-blind controlled clinical trials. Descriptive statistics are frequently used to help understand and gauge various characteristics of a drug. Inferential statistics helps quantify probabilities of successes and risks in drug discovery and development, as well as variability around those probabilities. Statistics is also an important decision-making tool throughout the entire drug development process. In clinical trials of all phases, studies are designed using statistical principles. Clinical data are displayed and analyzed using various statistical models.

1.2 New Drug Development Process

Most of the drugs available in pharmacy started out as a chemical compound or a biologic discovered in laboratories. When first discovered, this new compound or biologic is denoted as a drug candidate. Drug development is a process that starts when the drug candidate is first discovered, and continues until it is available to be prescribed by physicians to treat patients (Ting, 2003). A compound is usually a new chemical entity synthesized by scientists from drug companies (also referred as sponsors), universities, or research institutes. A biologic can be a protein, a part of a protein, DNA or a different form either extracted from tissues of another live body or cultured by some type of bacteria. In any case, this new compound or biologic will have to go through the drug development process before it can be used by the general public. For purposes of this book, the focus will mostly be on the chemical compound development.

The drug development process can be broadly classified into two major components: nonclinical development and clinical development. Nonclinical development includes all drug testing performed outside of the human body. The clinical development is based on experiments conducted in the human body. Nonclinical development can further be broadly divided into pharmacology, toxicology, and formulation. In these processes, experiments are performed in laboratories or pilot plants. Observations from cells, tissues, animal bodies, or drug components are collected to derive inferences for potential new drugs. Chemical processes are involved in formulating the new compound into drugs to be delivered into human

body. Clinical development can be further divided into Phases I, II, III, and IV. Clinical studies are designed to collect data from normal volunteers and subjects with the target disease, in order to help understand how the human body acts on the drug candidate, and how the drug candidate helps patients with the disease.

A new chemical compound or a biologic can be designated as a drug candidate because it demonstrates some desirable pharmacological activities in the laboratory. At the early stage of drug development, the focus is mainly on cells, tissues, organs, or animal bodies. Experiments on human beings are performed after the candidate passes these early tests and looks promising. Hence, nonclinical development may also be referred to as preclinical development since these experiments are performed before human trials.

Throughout the whole drug development process, two scientific questions are constantly being addressed: Does the drug candidate work? Is it safe? Starting from the laboratory where the compound is first discovered, the candidate has to go through lots of tests to see if it demonstrates both efficacy (the drug works) and safety. Only the candidates passing all those tests can be progressed to the next step of development. In the United States, after a drug candidate passes all of the nonclinical tests, an investigational new drug (IND) document is filed to the Food and Drug Administration (FDA). After the IND is approved, clinical trials (tests on humans) can then be performed. If this drug candidate is shown to be safe and efficacious through Phases I, II, and III of the clinical trials, the sponsor will file a new drug application (NDA) to the FDA in the United States. The drug can only be available for general public consumption in the United States, if the NDA is approved. Often, the approved drug is continually studied for safety and efficacy, for example, in different subpopulations. These post-marketing studies are generally referred as Phase IV of the clinical trials.

1.3 Nonclinical Development

1.3.1 Pharmacology

Pharmacology is the study of the selective biological activity of chemical substances on living matter. A substance has biological activities when, in appropriate doses, it causes a cellular response. It is selective when the response occurs in some cells and not in others. Therefore, a chemical compound or a biologic has to demonstrate these activities before it can be further developed. In the early stage of drug testing, it is important to differentiate an "active" candidate from an "inactive" candidate. There are screening procedures to select these candidates. Two properties of particular interest are sensitivity and specificity. Given that a compound is active, sensitivity is the conditional probability that the screen will classify it as positive. Specificity is the conditional probability that the screen will call a compound negative given that it is truly inactive.

Usually sensitivity and specificity can be a trade-off; however, in the ideal case, we hope both of these values be high and close to one.

Quantity of these pharmacological activities may be viewed as the drug potency or strength. The estimation of drug potency by the reactions of living organisms or their components is known as bioassay. According to Finney (1978), bioassay is defined as an experiment for estimating the potency of a drug, material, preparation, or process by means of the reaction that follows its application to living matters.

As discussed previously, one of the most important relationships needs to be studied for pharmacological activities is the dose–response relationship. In these experiments, several doses of the drug candidates are selected, and the responses are measured for each corresponding dose. After response data are collected, regression or nonparametric methods may be applied to analyze the results. As shown in Figure 1.2, the focus of nonclinical pharmacology is to help estimate the response curve at left. By increasing the dose or concentration of the drug candidate, if the pharmacological response does not change and stays at the low level of activity, then it can be concluded that this candidate does not have the activity under study and there is no need to develop this candidate. If the drug candidate is active, then the information about how much response can be expected for a given dosage (or concentration) can be used to help guide the design of dose selection clinical trials in human studies. Concerns relating to dose finding in nonclinical pharmacology are covered in Chapter 2.

1.3.2 Toxicology/Drug Safety

Drug safety is one of the most important concerns throughout all stages of drug development. In the preclinical stage, drug safety needs to be studied for a few different species of animals (e.g., mice, rabbits, rodents). Studies are designed to observe adverse drug effects or toxic events experienced by animals treated with different doses of the drug candidate. Animals are also exposed to the drug candidate for various lengths of time to see if there are adverse effects caused by cumulative dosing over time. These results are summarized and analyzed by using statistical methods. When the results of animal studies indicate potentially serious side effects, drug development is either terminated or suspended pending further investigations of the problem.

Depending on the duration of exposure to the drug candidate, animal toxicity studies are classified as acute studies, subchronic studies, chronic studies, and reproductive studies (Selwyn, 1988). Usually the first few studies are acute studies; i.e., the animal is given one or a few doses of the drug candidate. If only one dose is given, it can also be called a single-dose study. Only those drug candidates demonstrated to be safe in the single-dose studies can be progressed into multiple-dose studies. Single-dose acute studies in animals are primarily used to set the dose to be tested in chronic studies. Acute studies are typically about 2 weeks in duration. Repeat dose studies of 30 to 90 days duration are called subchronic studies. Chronic studies are usually designed with more than 90 days of duration. These studies are conducted in rodents and in at least one nonrodent species. Some chronic studies may also be viewed as carcinogenicity studies because the rodent

studies consider tumor incidence as an important endpoint. Reproductive studies are carried out to assess the drug's effect on fertility and conception; they can also be used to study drug effect on the fetus and developing offspring.

Data collected from toxicology studies will help estimate the curve on the right-hand side of Figure 1.2. The information are not only used to identify a NOAEL (No Observed Adverse Event Level) for the drug candidate; it can also help provide guidance as to what type of adverse events to be expected in human studies. Again, results obtained from animal toxicity studies are very useful in helping design dose selection clinical trials in humans. More details about drug toxicity and dose–response are also described in Chapter 2.

1.3.3 Drug Formulation Development

As discussed earlier, a potential new drug can be either a chemical compound or a biologic. If the drug candidate is a biologic, then the formulation is typically a solution, which contains a high concentration of such a biologic, and the solution is injected into the subject. On the other hand, if the potential drug is a chemical compound, then the formulation can be tablets, capsules, solution, patches, suspension, or other forms. There are many formulation problems that require statistical analyses. The formulation problems that stem from chemical compounds are more likely to involve widely used statistical techniques. The paradigm of a chemical compound is used here to illustrate some of these formulation-related problems and how they can be related to dose selection.

A drug is the mixture of the synthesized chemical compound (active ingredients) and other inactive ingredients designed to improve the absorption of the active ingredients. How the mixture is made depends on results of a series of experiments. Usually these experiments are performed under some physical constraints, e.g., the amount of supply of raw materials, capacity of container, size and shape of the tablets. In the early stage of drug development, drug formulation needs to be flexible so that various dose strengths can be tested in animals and in humans. Often in the nonclinical development stage or in early phase of clinical trials, the drug candidate is supplied in powder form or as solutions to allow flexible dosing. By the time the drug candidate progresses into late Phase I or early Phase II, fixed dosage form such as tablets, capsules, or other formulations are more desirable.

The dose strength depends on both nonclinical and clinical information. The drug formulation group works closely with laboratory scientists, toxicologists and clinical pharmacologists to determine the possible dose strengths for each drug candidate. In many cases, the originally proposed dose strengths will need to be changed depending on results obtained from Phase II studies. These formulations are developed for clinical trial usage and are often different from the commercial formulation. After the new drug is approved for market, commercial formulation should be readily available for distribution.

1.4 Premarketing Clinical Development

If a chemical compound or a biologic gets through the selection process from animal testing and is shown to be safe and efficacious to be tested in human, it progresses into clinical development. In drug development for human use, the major distinction between "clinical trials" and "nonclinical testing" is the experimental unit. In clinical trials, the experimental units are human beings, and the experimental units in "nonclinical testing" are nonhuman subjects. As mentioned earlier, the results of these nonclinical studies will be used in the IND submission prior to the first clinical trial. If there is no concern from the FDA after 30 days of the IND submission, the sponsor can then start clinical testing for this drug candidate. At this stage, the chemical compound or the biologic may be referred to as the "test drug" or the "study drug".

An IND is a document that contains all the information known about the new drug up to the time the IND is prepared. A typical IND includes the name and description of the drug (such as chemical structure, other ingredients); how the drug is processed; information about any preclinical experiences relating to the safety of the drug; marketing information; past experiences or future plans for investigating the drug both in the United States and in foreign countries. In addition, it also contains a description of the clinical development plan (CDP, refer to Section 1.5). Such a description should contain all of the informational materials to be supplied to clinical investigators, signed agreements from investigators, and the initial protocols for clinical investigation.

Clinical development is broadly divided into four phases, namely Phases I, II, III, and IV. Phase I trials are designed to study the short-term effects; e.g., pharmacokinetics (PK, what does a human body do to the drug), pharmacodynamics (PD, what does a drug do to the human body), and dose range (what range of doses should be tested in human) for the new drug. Phase II trials are designed to assess the efficacy of the new drug in well-defined subject populations. Dose–response relationships are also studied during Phase II. Phase III trials are usually long-term, large-scale studies to confirm findings established from earlier trials. These studies are also used to detect adverse effects caused by cumulative dosing. If a new drug is found to be safe and efficacious from the first three phases of clinical testing, an NDA is filed for the regulatory agency (FDA, in the United States) to review. Once the drug is approved by the FDA, Phase IV (postmarketing) studies are planned and carried out. Many of the Phase IV study designs are dictated by the FDA to examine safety questions; some designs are employed to establish new uses.

1.4.1 Phase I Clinical Trials

In a Phase I PK study, the purpose is usually to understand PK properties and to estimate PK parameters (e.g., AUC, Cmax, Tmax, to be described in next paragraph) of the test drug. In many cases, Phase I trials are designed to study the bioavailability of a drug, or the bioequivalence among different formulations of

the same drug. "Bioavailability" means "the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed and becomes available at the site of drug action" (Chow and Liu, 1999). Experimental units in such Phase I studies are mostly normal volunteers. Subjects recruited for these studies are generally in good health.

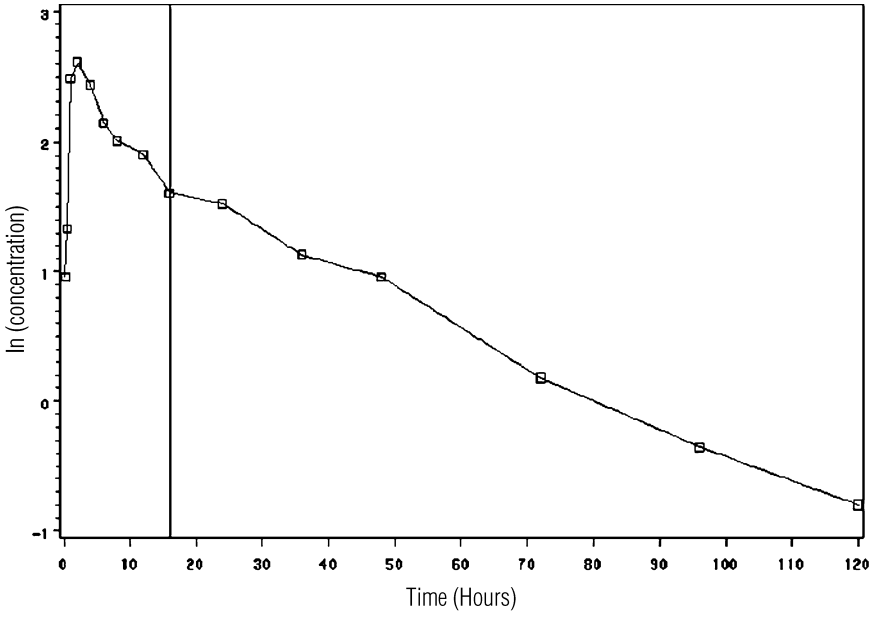

Figure 1.4. Drug concentration–time curve.

A bioavailability or a bioequivalence study is carried out by measuring drug concentration levels in blood or serum over time from participating subjects. These measurements are summarized into one value per subject per treatment period. These summarized data are then used for statistical analysis. Figure 1.4 presents a drug concentration–time curve. Data on this curve are collected at discrete time points. Typical variables used for analysis of PK activities include area under the curve (AUC), maximum concentration ($C_{\max}$), minimum concentration ($C_{\min}$), time to maxium concentration ($T_{\max}$), and others. These variables are computed from drug concentration levels as shown in Figure 1.4. Suppose AUC is used for analysis, then these discretely observed points are connected (for each subject under each treatment period) and the AUC is estimated using a trapezoidal rule. For example, AUC up to 24 hours for this curve is computed by adding up the areas of the triangle between 0 hour and 0.25 hour, the trapezoid between 0.25 hour and 0.5 hour, and so on, and the trapezoid between 16 hour and 24 hour. Usually the AUC and $C_{\max}$ are first transformed using natural log, then they are included in the data analysis. Chapter 6 discusses how PK data and PK/PD models can be used to help dose selection in Phase II.

Statistical designs used in Phase I bioavailability studies are often crossover designs; i.e., a subject is randomized to be treated with formulation A first, and then treated with formulation B after a "wash-out" period; or randomized to formulation B first, and then treated with A after wash-out. In some complicated Phase I studies, two or more treatments may be designed to cross several periods for each subject. Advantages and disadvantages of crossover designs are discussed in Chow and Liu (1999). Response variables including AUC and $C_{\max}$ are usually analyzed using ANOVA models. Random and mixed effects linear/nonlinear models are also commonly used in the analysis for Phase I clinical studies. In certain designs, covariate terms considered in these models can be very complicated. How Phase I studies can help in dose finding are discussed in Chapter 3.

1.4.2 Phase II/III Clinical Trials

Phase II/III trials are designed to study the efficacy and safety of a test drug. Unlike Phase I studies, subjects recruited in Phase II/III studies are patients with the disease for which the drug is developed. Response variables considered in Phase II/III studies are mainly efficacy and safety variables. For example, in a trial for the evaluation of hypertension (high blood pressure), the efficacy variables are blood pressure measurements. For an anti-infective trial, the response variables can be the proportion of subjects cured or time to cure for each subject. Phase II/III studies are mostly designed with parallel treatment groups (in contrast to crossover). Hence, if a patient is randomized to receive treatment A, then this patient is to be treated with Drug A through out the whole study.

Phase II trials are often designed to compare one or a few doses of a test drug against placebo. These studies are usually short-term (several weeks) and designed with a small or moderate sample size. Often, Phase II trials are exploratory in nature. Patients recruited for Phase II trials are somewhat restrictive; i.e., they tend to be with certain disease severity (not too severe and not too mild), without other underlying diseases, and not on background treatments. One of the most important types of Phase II study is the dose–response study. As expressed on the left curve of Figure 1.1, drug efficacy may increase as dose increases. In a dose–response study, the following fundamental questions need to be addressed (Ruberg, 1995):

- Is there any evidence of a drug effect?
- What doses exhibit a response different from the control response?
- What is the nature of the dose–response relationship?
- What is the optimal dose?

Typical dose–response studies are designed with fixed doses, parallel treatment groups. For example, in a four-treatment group trial designed to study dose–response relationships, three test doses (low, medium, high) are compared against placebo. In this case, results may be analyzed using multiple comparison techniques or modeling approaches. In general, Phase II studies are carried out for an estimation purpose. Dose–response study designs used in Phase II are discussed

in Chapters 6, 7, and 8. A special chapter (Chapter 14) is devoted for discussion on power and sample size issues.

Phase III trials are long-term (can last up to a few years), large-scale (several hundreds of patients), with less restrictive patient populations, and often compared against a known active drug (in some cases, compared with placebo) for the disease to be studied. Phase III trials tend to be confirmatory trials designed to verify findings established from earlier studies.

Statistical methods used in Phase II/III clinical studies can be different from those used for Phase I or nonclinical studies. Statistical analyses are selected based on the distribution of the variables and the objectives of the study. Many Phase I analyses tend to be descriptive, with estimation purposes. In Phase II/III, categorical data analyses are frequently used in analyzing count data (e.g., number of subjects responded, number of subjects with a certain side effect, or number of subjects improved from "severe symptom" to "moderate symptom"). Survival analyses are commonly used in analyzing time to an event (time to discontinuation of the study medication, time to the first occurrence of a side effect, time to cure). Regression analyses, t tests, analyses of variance (ANOVA), analyses of covariance (ANCOVA), and multivariate analyses (MANOVA) are useful in analyzing continuous data (blood pressure, grip strength, forced expiration volume, number of painful joints, AUC, and others). In many cases, nonparametric analytical methods are selected because the data do not fit any known parametric distribution well. In some other cases, the raw data are transformed (log-transformed, ranked, centralized, combined) before a statistical analysis is performed. A combination of various statistical tools may sometimes be used in a drug development program. Hypothesis tests are often used to compare results obtained from different treatment groups. Point estimates and interval estimates are also frequently used to estimate subject responses to a study medication or to demonstrate equivalence between two treatment groups. Statistical methods for analyzing dose–response studies are introduced in Chapters 9–13.

Although the recommendation of doses is primarily made during Phase II, in most of the cases, dose selection is further refined in Phase III. One reason for this is that Phase III exposure is long-term and with a large patient population. From an efficacy point of view, the drug efficacy from recommended doses may or may not sustain after longer duration of treatment. More importantly, from a safety point of view, a safe dose selected from Phase II results may lead to some other safety concerns after this dose is exposed for a longer time. One possibility is that drug accumulation over time may cause additional adverse events. Therefore, it is a good practice to consider incorporating more doses than just the target dose(s) in Phase III. It helps to have a dose higher than the target dose(s) so that in case the target dose(s) is not as efficacious as anticipated, we can consider this higher dose to be the effective dose. It is also useful to have a dose lower than the target dose(s) so that in case the target dose is not safe and the lower dose can be considered as a viable alternative.

After a clinical study is completed, all of the data collected from this study are stored in a database and statistical analyses are performed on data sets

extracted from the database. A study report is prepared for each completed clinical trial. It is a joint effort to prepare such a study report. Statisticians, data managers, and programmers work together to produce tables, figures, and statistical reports. Statisticians, clinicians, and technical writers will then put together clinical interpretations from these results. All of these are incorporated into a study report. Study reports from individual clinical trials will eventually be culled as part of an NDA.

1.4.3 Clinical Development for Life-Threatening Diseases

In drug development, concerns for drugs to treat life-threatening diseases, such as cancer or AIDS, can be very different from those for other drugs. In the early stage of developing a cancer drug, patients are recruited to trials under open-label treatment with test drug and some effective background cancer therapy. Under this circumstance, doses of the test drug may be adjusted during the treatment period. Information obtained from these studies will then be used to help suggest dose regimen for future studies. Various study designs to handle these situations are available in statistical/oncology literatures. Examples of these types of flexible designs are covered in Chapters 4 and 5.

In some cases, drugs for life-threatening diseases are approved for the target patient population before large-scale Phase III studies are completed because of public need. When this is the case, additional clinical studies may be sponsored by National Institute of Health (NIH) or National Cancer Institute (NCI) in the United States. Many of the NIH/NCI studies are still designed for dose finding or dose adjustment purposes.

1.4.4 New Drug Application

When there is sufficient evidence to demonstrate a new drug is efficacious and safe, an NDA is put together by the sponsor. An NDA is a huge package of documents describing all of the results obtained from both nonclinical experiments and clinical trials. A typical NDA contains sections on proposed drug label, pharmacological class, foreign marketing history, chemistry, manufacturing and controls, nonclinical pharmacology and toxicology summary, human pharmacokinetics and bioavailability summary, microbiology summary, clinical data summary, results of statistical analyses, benefit–risk relationship, and others. If the sponsor intends to market the new drug in other countries, then packages of documents will need to be prepared for submission to those corresponding countries, too. For example, a new drug submission (NDS) needs to be filed to Canadian regulatory agency and a marketing authorization application (MAA) needs to be filed to the European regulatory agencies.

Often, an NDA is filed while some of the Phase III studies are ongoing. Sponsors need to be very careful in selecting the "data cut-off date" because all of the clinical data in the database up to the cut-off date need to be frozen and stored so that NDA study report tables and figures can be produced from them. The data sets stored in

such an "NDA database" may have to be retrieved, and reanalyzed after filing, in order to address various queries from regulatory agencies. After these data sets are created and stored, new clinical data can then be entered into the ongoing database.

An NDA package usually includes not only individual clinical study reports, but also combined study results. These results may be summarized using meta-analyses or pooled data analyses on individual patient data across studies. Such analyses are performed on efficacy data to produce summary of clinical efficacy (SCE, also known as integrated analysis of efficacy—IAE) and on safety data to produce the summary of clinical safety (SCS, also known as integrated analysis of safety—IAS). These summaries are important components of an NDA. Increasingly, electronic submissions are filed as part of the NDA. Electronic submissions usually include individual clinical data, programs to process these data, and software/hardware to help reviewers from FDA or foreign regulatory agencies in reviewing the individual data as well as the whole NDA package.

1.5 Clinical Development Plan

In the early stage of drug development, as early as in the nonclinical stage, a clinical development plan (CDP) should be drafted. This plan should include clinical studies to be conducted in Phases I, II and III. The CDP should be guided by the draft drug label. The drug label provides detailed information on how the drug should be used. Hence, a draft label at the early stage of drug development lays out the target profile for the drug candidate. Clinical studies should be designed to help obtain information that will support this given target drug label.

One of the most important aspects of labeling information is the recommended regimen for this new drug. The regimen includes dosage and dose frequency. In the early stage of drug development, scientists need to predict the dosage and frequency as to how the drug will be labeled. Based on this prediction, the clinical development program should be designed to obtain necessary information that will support the recommended regimen. For example, if the drug will be used with one fixed dose, then the CDP should propose clinical studies to help find that dose. On the other hand, if the drug will be used as titration doses, then studies need to be designed to study the dose range for titration.

Another example is dosing frequency. Patients with chronic diseases tend to take multiple medications every day. Many patients may prefer a once-a-day (QD) drug or a twice-a-day (BID) drug. In early development of a new drug, if the best marketed product for the target disease is prescribed as a twice-a-day drug, and the preliminary information of this test drug indicates that it will have to be used three or more times a day, then the CDP needs to include studies to reformulate the test drug so that it can be used as a twice-a-day drug or a once-a-day drug, before it can be progressed into later phases of development.

A CDP is an important document to be used during the clinical development of a new drug. As a drug progresses in the clinical development process, the CDP should be updated to reflect the most current information about the drug and

depending on the findings up to this point in time, the sponsor can assess whether a new version of drug label should be drafted. In case a new draft of drug label is needed, the development plan should be revised so that studies can be planned to support the new drug label.

The overall clinical development process can be viewed in two directions as shown in Figure 1.5. One is the forward scientific process, as more data and information are accumulating, we know more about the drug candidate and we design later phase studies to help progress the candidate. On the other hand, the planning is based on the draft drug label. From the draft label, we have a target profile for the drug. Depending on the drug properties to be demonstrated on the label, the sponsor needs to have Phase III studies to support those claims. In order to collect information to help design those Phase III studies, data need to be available for the corresponding Phase I or Phase II studies. Therefore, the thinking process is backward by looking at the target profile first, and then prepares the CDP according to the draft label.

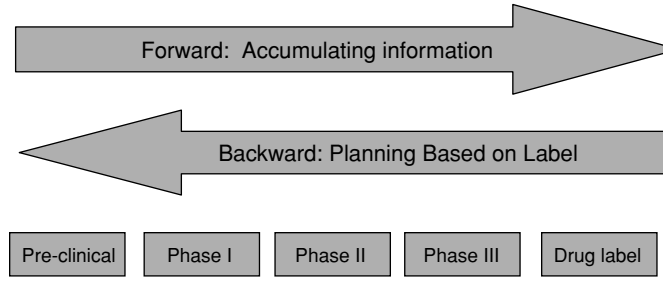

Figure 1.5. Clinical development process.

1.6 Postmarketing Clinical Development

An NDA serves as a landmark of the drug development. The development process does not stop when an NDA is submitted or approved. However, the objectives of the process are changed after the drug is approved and is available on the market. Studies performed after the drug is approved are typically called postmarketing studies, or Phase IV studies.

One of the major objectives in postmarketing development is to establish a better safety profile for the new drug. Large-scale drug safety surveillance studies are very common in Phase IV. Subjects/patients recruited in Phases I, II, and III are often somewhat restricted (patients would have to be within a certain age range, gender, disease severity or other restrictions). However, after the new drug is approved and is available for the general patient population, every patient with the underlying disease can be exposed to this drug. Problems related to drug safety that have not been detected from the premarketing studies (Phases I, II, and III) may now be observed in this large, general population.

Another objective of a Phase IV study is for the sponsor to increase the market potential for the new drug by demonstrating an improvement in patients' quality of life (QoL) and by establishing its economic value. Studies designed to achieve this objective include QoL studies and pharmaco-economic studies. Studies of this nature are often referred to as "outcomes research" studies. One of the main differences between a QoL study and an efficacy/safety study is the type of variables being studied. Although in many cases, a QoL study may include ordinary efficacy and safety endpoints, such a study will also include QoL-specific variables. These variables are typically collected from questionnaires designed for the patient to evaluate the change in life style caused by the disease and the improvement (of quality of life) brought by the medication. In general, clinical efficacy variables are measured to study the severity of symptoms, and quality of life variables are measured to study how a patient copes with life while experiencing the underlying disease. In the United States, the FDA determines whether to approve the drug based on efficacy and safety findings. However, a patient may prefer a particular drug based on how that patient feels. Among the drugs approved by FDA for the same disease, the patient tends to choose the one that is better for his/her quality of life.

Traditionally, Phase I, II, and III studies are used to establish the efficacy and safety of a drug, and Phase IV is used to study QoL. Recently, there are many changes in the field of outcomes research. For example, the new name of many of these variables is "patient reported outcome (PRO)". Generally, PRO includes more variables than just QoL. Another important change is that more and more Phase II/III studies are designed to collect and analyze PRO data. Furthermore, FDA and other regulatory agencies are more involved in reviewing and labeling PRO findings.

Pharmaco-economic studies are designed to study the direct and indirect cost of treating a disease. In these studies, costs of various FDA approved drugs are compared. Costs may include the price of the medication, expenses for monitoring the patient (physician's charge, costs of lab tests, etc.), costs for treating side effects caused by a treatment, hospital charges, and other items. Analyses are performed on these studies to demonstrate the cost-effectiveness. By showing that the new drug overall costs less than another drug from a different company, the sponsor can increase the competitive advantage by marketing this new drug.

Results obtained from "outcomes research" studies can be used by the pharmaceutical company to promote the new drug. For example, if the new drug is competing against another drug treating the same disease, the company may be able to show that the new drug improved the patient's quality of life beyond the improvement provided by the competing medication. Based on the results from the pharmaco-economic studies, the company may also be able to demonstrate that the new drug brought overall savings to both the patients and the insurance carriers. These studies help evaluate other properties or characteristics of the new drug in addition to its medical value. The results from these studies may be used to increase the market potential for the new drug.

Finally, another type of study frequently found during the postmarketing stage is the study designed to use the new drug for additional indications (symptoms or diseases). A drug developed for disease A may also be useful for disease B, but the pharmaceutical company may not have sufficient resources (budget, manpower, etc.) to develop the drug for both indications at the same time. In this case, the sponsor may decide to develop the drug for disease A to obtain approval for drug to be on the market first, and then develop it to treat disease B. There are also other situations that this strategy can be useful. Hence, Phase III, IV studies designed for "new indications" are very common.

Occasionally, in postmarketing studies, we may see that a drug is efficacious at a lower dose than the dosage recommended in the drug label. This lower dose tends to provide a better safety profile. When this is the case, drug label could be changed to include the lower dose as one of the recommended doses. On the other hand, it is seen that the recommended dose may work for many patients, but the dose is not high enough for some other patients. When this is the case, an increase in dose may be necessary. Based on Phase IV clinical trials, if there is a need to label a higher dose, the sponsor would negotiate with the regulatory agencies to modify the drug label to allow a higher dose to be prescribed.

1.7 Concluding Remarks

Based on the drug development process described above, it is obvious that selecting the right dose for a new drug is a very important process. Without dose information, it is not possible for a physician to prescribe the drug to patients. One of the regulatory guiding documents describing the importance and practical difficulties in the study of the dose–response relationship is ICH (International Conference on Harmonization) E4 (1994) Guidance. Readers are encouraged to refer to this document for some of the regulatory viewpoints.

Studying and understanding the dose–response relationship for a new drug is an evolving, nonstop process. It started at the time when the new drug was first discovered in the laboratory. Unless this newly discovered compound shows increasing activities as the concentration increases, it would not be progressed into further development. This increasing relationship is continually studied in tissues, in animals, and eventually in humans. Phase I clinical trials are designed to collect information that will support the study of dose–response relationship for Phase II. Dosing information is one of the most important considerations in Phases II and III clinical studies. Finally, before, during and after the NDA process, dose selection is being considered by the sponsor, the regulatory agencies, and the general public. Even after the drug is approved and available on the market, new drug doses are still studied carefully and the level of investigation depends on responses observed from the general patient population. When necessary, dose adjustment based on postmarketing information is still a common practice.

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