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Quantitative Decisions in Drug Development

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Christy Chuang-Stein
To my parents, Bruce, Terresa, and Isaac

Simon Kirby
To Dad, Mum, Katie, Theo, Helen,
Rob, and Andy

Preface

Developing a new drug is a high-risk and high-reward enterprise. The high risk is reflected by the generally low success rate of turning a new molecular entity into an approved drug. The success rate has fluctuated over time and has also varied across therapeutic areas. While the success rate has improved in recent years for cancer drugs due to the advent of targeted therapies, the rate has been disappointingly low for certain disorders such as Alzheimer's disease.

In addition to the high risk, the cost of developing a new drug has increased at a pace faster than inflation. Tufts Center for the Study of Drug Development has published a series of reports examining the average pretax industry cost to bring a new medicine to the market. The most recent report, published in 2014, estimated an average cost around 2.56 billion USD in 2013 money. By comparison, in 2003, the cost was about 1.04 billion USD in 2013 money, based on the same method of calculation. While some researchers have questioned these figures, these reports nevertheless show a substantial increase in the cost of drug development over a decade.

The low success rate and the high cost have motivated many pharmaceutical companies to look for better methods to make portfolio decisions including whether to invest in a particular new molecular entity and how to make Go/No-Go decisions. Since the majority of development programs are likely to fail, it is important to be able to terminate a program with a low probability of success as early as possible.

Making efficient decisions requires designing efficient trials. Developing innovative designs that can enable good quantitative decisions at the earliest time possible has been the focus of much research in recent years. Many books have been written about clinical trial designs to support drug development. Therefore, we have decided to focus on methods for making quantitative decisions in this book. Because of the inseparable relationship between designs and decisions, we also spend a good portion of this book discussing design options.

At Pfizer, the journey to quantitative decisions began during the first decade of the twenty-first century. The implementation began with proof-of-concept studies. Teams designing these early studies were required to present, to a technical review

committee, the operating characteristics of their trials/decision rules with respect to the target product profile. The move to assess the probability of success in late-stage trials was firmly in place by the year 2010 with the establishment of a Probability of Technical and Regulatory Success (PTRS) Council.

Many statisticians and scientists played a critical role in the above journey. The input from commercial colleagues helped solidify the need to quantitatively incorporate the target product profile when designing a trial and setting up the subsequent decision rule. We have learned a great deal from the early pioneer advocates at Pfizer. Their work inspired us to write this book. We are particularly indebted to Mike Brown, Alan Clucas, Vlad Dragalin, Wayne Ewy, Bradley Marchant, Ken Kowalski, Mike K Smith, Jonathan French, Cyrus Hoseyni, Richard Lalonde, Scott Marshall, Peter Milligan, Mohan Beltangady, Phil Woodward, Joanna Burke, Neal Thomas, and Liam Ratcliffe for their scientific and organizational leadership.

The book has 13 chapters. Chapter 1 offers a high-level overview of clinical testing and regulatory review of a pharmaceutical product. Chapter 2 reviews the Frequentist approach to the testing of hypotheses and in particular the two-action decision problem. In the context of drug development, the two actions correspond to progressing or not progressing a drug for further development. Chapter 3 discusses the metrics commonly used to characterize the performance of a diagnostic test. Chapter 4 draws an analogy between successive trials conducted during the clinical testing of an investigational product and a series of diagnostic tests. Under this analogy, the condition to diagnose by a clinical trial is the existence of a clinically meaningful effect of the investigational product. We have found this analogy particularly useful to explain to our nonclinical colleagues why replication is such an important concept in drug development and to show why replication is not as easy as many people might hope.

The predictive power of a diagnostic test depends on the existing information concerning the prevalence of the condition to be diagnosed in a relevant population. Similarly, the predictive power of a clinical trial depends on available prior knowledge concerning the investigational product. Articulating such prior knowledge is the topic of Chap. 5. In Chap. 6, we describe metrics that are useful to evaluate designs and associated decision rules for efficacy assessment at various stages of premarketing development. The focus on efficacy is due to the generally well-defined endpoints to decide the beneficial effect of a new drug. Chapter 7 covers the proof-of-concept stage, while Chaps. 8 and 9 cover the dose-response and confirmatory stage, respectively.

Chapter 10 focuses on assessing the design of a trial for comparative effectiveness assessment. By comparative effectiveness, we mean the comparison of different active treatments to determine which treatment works best. This focus reflects the increasing importance of these comparisons in the market place due to the need to justify the price and to qualify for reimbursement.

The metrics used in Chaps. 7–10 do not include any cost consideration explicitly. But, cost is an integral part of drug development strategy optimization. Incorporating cost into design consideration is the topic of Chap. 11 with two example approaches. The first one optimizes a benefit-cost efficiency score that

measures the cost-effectiveness of a proof-of-concept trial design. The second approach combines costs and potential commercial returns to assess drug development options. The chapter includes a detailed discussion on the calculation of the expected net present value which could be of interest to readers without much exposure to product valuation.

In Chap. 12, we examine the bias that can be produced by the use of Phase 2 results that have been selected because of a favorable outcome. We have hinted at this source of bias in earlier chapters and have dedicated Chap. 12 to this issue. We offer recommendations on how to correct for this bias when using prior positive results to design the next trial.

In the final chapter of the book, we include selected topics that affect design and decision choices at all stages of drug development. Examples include adaptive designs, benefit-risk, and economic assessment. These are all active research areas. Even though we offer some references, it is not our intent to cover these areas in detail in this book.

The book is written for readers with a broad range of responsibilities in drug development. While the book contains a lot of technical details for quantitative scientists, it also contains plenty of concepts presented in a unified framework which, we believe, can help less quantitative readers make more quantitative decisions.

We hope you will enjoy reading the book as much as we did writing it.

Kalamazoo, MI, USA — Christy Chuang-Stein
Cambridge, UK — Simon Kirby
May 2017

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Chapter 1
Clinical Testing of a New Drug

Nearly 60 percent of Americans—the highest ever—are taking prescription drugs.
Washington Post, November 3, 2015

1.1 Introduction

A research study reports an increase in the overall use of prescription drugs among adults (those $\geq$20 years old) between 2011 and 2012 from that between 1999 and 2000 in the United States (USA) (Kantor et al. 2015). In 1999–2000, an estimated 51% of the US adults reported using any prescription drug. The estimated figure for 2011–2012 is 59%. During the same period, the prevalence of polypharmacy (use of $\geq$5 prescription drugs) increased from 8.2 to 15%. Many factors contribute to this increase, factors such as better disease prevention and management, lifestyle change, an aging population, and an increase in the percentage of people who are either overweight or obese. The number of new prescription drugs developed and approved for public use every year has also greatly contributed to this increase.

Developing a new drug is a high-risk and high-reward enterprise. The high risk is reflected by the low success rate of turning a new molecular entity (NME) into an approved drug. The success rate fluctuated over time and varied across therapeutic areas. For example, the US Food and Drug Administration published the Critical Path Initiative document in 2004 (FDA 2004), in which FDA quoted a "current" success rate around 8% and a historical success rate of 14%.

Understandably, the success rate varies substantially across therapeutic areas (DiMasi et al. 2010, 2013). For example, the success rate of drugs for treating common bacterial infections is generally higher than that for drugs treating disorders of the central nervous system. This is in part due to the heavy use of the minimum inhibitory concentration (MIC) to help determine the appropriate dose and schedule for an NME for bacterial infections. For a microorganism studied in vitro, the MIC for an antibacterial agent is the lowest concentration of the agent which prevents detectable growth of the organism in agar or broth media under

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standardized conditions (Clinical and Laboratory Standards Institute 2003). In addition to MIC, animal models can be used to predict human response to an NME for many infections (Leggett et al. 1989; Craig 2003). So, if an NME could deliver the desired MIC coverage without causing unacceptable side effects and if the animal model shows promising results, the NME will likely become a viable treatment option.

The success rate discussed above pertains to the clinical testing of an NME in humans. However, after an NME is synthesized, it will first be screened for biologic and pharmacologic activities. Preclinical testing in animals follows the biologic and pharmacologic screening. Preclinical testing is necessary before an NME can be tested in humans. Besides the need to understand the pharmacokinetic (PK) profile of the NME in animals, preclinical evaluation assesses the NME for its general toxicity, cardiac liability, carcinogenicity, and reproductive toxicity. Some of the assessment could be done in vitro, but most is done in vivo using different animal species. The International Council for Harmonisation (ICH) published a series of guidance documents on the technical requirements for preclinical safety evaluation of pharmaceuticals for human use. If preclinical testing suggests a reasonable PK and toxicity profile at doses likely to be used by target patients, then the NME will enter into the clinical testing stage.

Researchers have offered substantially different estimates for the success rates for the discovery and preclinical testing stages. For example, Bains (2004) estimated an approximately 30% cumulative success rate for discovery and preclinical testing combined, while Hill (2008) stated a $<1\%$ success rate. Despite the difference, it is clear that the failure rate during the preclinical stage of drug development is not negligible.

In addition to the high risk, the cost of developing a new drug has increased at a faster pace than inflation. A study released by the Tufts Center for the Study of Drug Development in 2014 suggests that the average pretax industry cost to bring a new medicine to market was around USD2.56 billion in 2013 money (DiMasi et al. 2014). The study included 106 investigational new drugs from ten mid- to large-size pharmaceutical companies, and the drugs were first tested in humans during 1995–2007. Cost included clinical development up to 2013. By comparison, in 2003, the cost was about USD1.04 billion in 2013 dollars. While some researchers questioned these figures, the latest study used the same approach as that used in the previous one (DiMasi et al. 2003) in estimating the development cost. The latest study shows a substantial increase in the drug development cost over a 10-year period.

The low success rate and the high cost have motivated many pharmaceutical companies to look for better methods to make portfolio decisions. Such decisions include whether to invest in a particular NME and how to make Go/No-Go decisions concerning a particular development program. Since most development programs are likely to fail, it is important to be able to terminate a program that has a low probability to succeed as early as possible. Making efficient decisions requires designing efficient trials to acquire the needed evidence. Developing

innovative designs that can enable good quantitative decisions at the earliest time has been the focus of much research in recent years.

Many books have been written about clinical trial designs to support drug development. Therefore, we will focus on methods for making quantitative decisions in this book. Because of the inseparable relationship between designs and decisions, we will also spend a good portion of this book on clinical trial designs.

In this chapter, we will offer a high-level review of clinical testing of a pharmaceutical product. We will first discuss in Sect. 1.2 the four distinct phases of clinical testing under a traditional development plan. We will discuss deviations from the traditional development plan and new regulatory approval pathways in Sect. 1.3. Section 1.4 offers some examples of recent advancements in clinical trial designs. We will conclude the chapter with a short summary in Sect. 1.5.

1.2 Clinical Development

Clinical testing of an NME to support its marketing authorization is often characterized by four phases as shown in Fig. 1.1. With some exceptions described in Sect. 1.3, three of the four phases occur before the NME is approved for marketing (premarketing) and the remaining one is afterward (postmarketing). The four phases are conveniently labeled as Phase 1, Phase 2, Phase 3, and Phase 4. A good description of the four phases can be found in an FDA guidance document (FDA 1997).

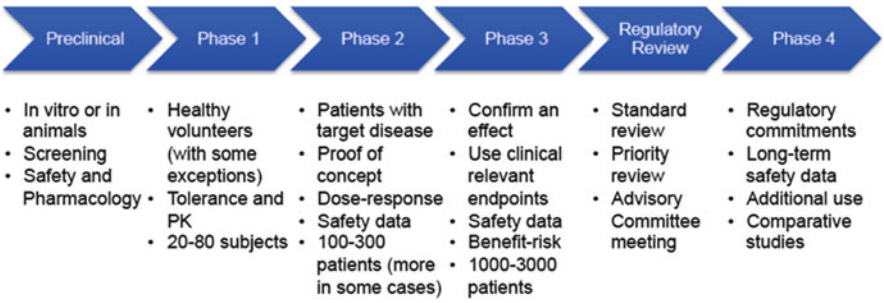

Fig. 1.1 The four phases of clinical testing

1.2.1 Phase 1

Phase 1 trials are where an NME is first tested in human subjects. These trials are designed to investigate what the human body does to an NME in terms of absorption, distribution, metabolism, and excretion (ADME). These are the pharmacokinetic (PK) properties of the NME. The investigation is typically conducted in healthy human volunteers, except for cytotoxic drugs. For cytotoxic drugs, Phase 1 is generally conducted in patients with very few therapeutic options due to the anticipated toxicities. When a drug is designed to target a receptor, Phase 1 trials can include an investigation of what the NME does to the receptor also.

Phase 1 trials in healthy subjects generally consist of single- and multiple-ascending-dose cohorts. Trials studying the effect of a single dose on subjects typically precede trials studying the effect of multiple doses. Some development plans stack single-dose and multiple-dose studies in such a way that there is a lag between exposing subjects to a single dose and exposing separate patients multiple times to the same dose. This strategy is shown in Fig. 1.2.

Besides collecting blood samples for PK analysis, Phase 1 trials investigate the common adverse reactions to an NME and what would be the NME's dose-limiting toxicities. We use the word "common" because the small number of subjects at this stage does not offer much opportunity to observe rare drug reactions. A typical ascending-dose trial (single dose or multiple doses) randomizes subjects to a fixed dose or a control within a cohort. Observations from a cohort will be assessed to decide if another cohort should be recruited to investigate the next higher dose in a prespecified dose range. The allowed dose range for Phase 1 testing is determined by the doses studied and adverse reactions observed in animal models.

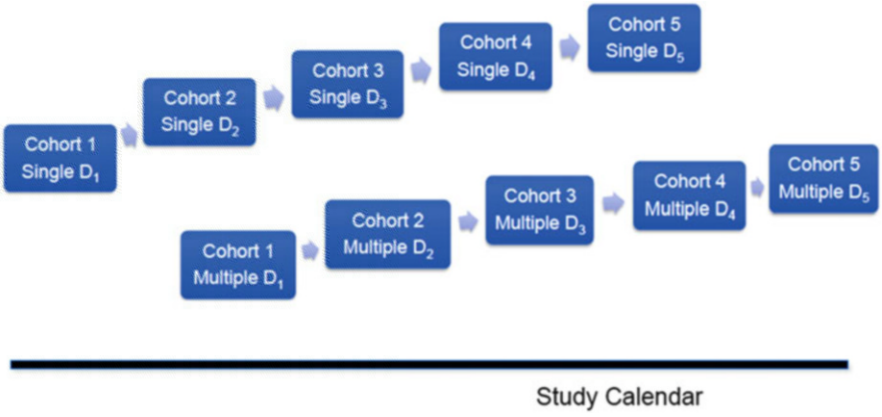

Fig. 1.2 Interwoven single- and multiple-ascending-dose studies

If the NME's overall safety profile observed in Phase 1 is judged to be acceptable relative to its potential (and yet to be observed) benefit, the development will progress to the second stage (Phase 2). The number of volunteers included in Phase 1 single- and multiple-ascending-dose studies typically ranges between 20 and 80, but could be higher if Phase 1 includes an assessment of the NME's mechanism of action or an early investigation of the NME's efficacy. The latter is a frequent feature of Phase 1 cancer trials. In these trials, a cohort of patients is often recruited at the maximum tolerated dose (MTD) to assess the NME's efficacy once the MTD is established. A good reference on designs for Phase 1 cancer trials is the book by Cheung (2011).

Other trials with a strong PK focus conducted early in the development process include bioavailability studies, drug-drug interaction studies, food effect studies, and PK studies in special populations such as subjects with impaired hepatic or renal functions. Understanding an NME's PK properties in individuals with hepatic or renal function is particularly important when an NME is excreted from the body through the liver or kidneys. Understanding how the body reacts to the NME under many different, yet important, conditions is important to the planning of subsequent trials.

1.2.2 Phase 2

Phase 2 investigates what a drug does to a patient with a target disorder (i.e., pharmacodynamics of the drug). Clinical trials at this stage are also designed to determine dose(s) whose benefit-risk profile warrants further investigation later in a confirmatory setting. Multiple doses within the dose range identified from Phase 1 are studied at this stage.

Phase 2 is typically the time when a manufacturer first learns of the beneficial effect of an NME. This stage has the highest attrition rate among the three premarketing phases. Therefore, if an NME is not likely to become a treatment option, it will be best to recognize this fact as soon as possible and stop further testing of the NME for the disorder already investigated. This objective plus fewer regulatory requirements at this stage offers opportunities for out-of-the-box thinking.

Testing in Phase 2 can be further divided into two stages. The first stage aims to establish the proof of concept (POC) of the NME, using a high dose (e.g., the maximum tolerated dose identified in Phase 1) to investigate the NME's efficacy. Occasionally, a sponsor may use a biomarker to verify the conjectured mechanism of the NME in a proof of mechanism (POM) study. If the study cannot establish a positive POM or POC, development of the NME in its current formulation for the indication under study will stop. Because an NME is often created with the objective to treat multiple disorders, discontinuing the development for one disorder does not

necessarily mean terminating the development altogether. We have seen this in the oncology area where an NME may be targeted for multiple cancer types (e.g., breast, lung, and renal).

Following a positive POC, an NME will be further tested in a dose-ranging study. A dose-ranging study typically includes a control and multiple doses of the NME. A placebo is often used as the control at this stage. The new NME and the placebo could be used alone as a monotherapy or added to a patient's background therapy.

This two-step process is often referred to as Phase 2a and Phase 2b (Sheiner 1997). To minimize the work necessary to initiate sites and obtain approvals from multiple institutional review boards, some sponsors have opted to combine the POC and the dose-response studies into one study with an unblinded interim analysis at the end of the POC stage. The sponsors will review results from the POC stage and may choose to use only data from the second stage to estimate the dose-response relationship. This strategy has the potential to increase operational efficiency by reducing the waiting period between Phase 2a and Phase 2b.

Depending on the target disorders, Phase 2 testing for a single disorder may consist of 100–300 patients. Despite strong advocacy by researchers like Sheiner (1997) to use a modeling approach to analyzing dose-response data, some sponsors continue to rely on pairwise comparisons to design and analyze dose-response studies. There have been renewed emphases from experts that the selection of dose(s) should be regarded as an estimation problem and handled by a modeling approach (EMA Dose Response Workshop 2014). Recent research (Pinheiro et al. 2010; Thomas et al. 2014) has shown that 300 patients in a dose-ranging study may not be enough to adequately identify the optimal dose based on a preset criterion.

Ideally, Phase 2 studies should use the same endpoints to assess the benefit associated with a dose as those to be used later in Phase 3. Unfortunately, this is not always possible because the endpoint needed for Phase 3 such as survival and serious morbidity may take a long time to obtain. In such a case, Phase 2 trials will use a short-term endpoint that hopefully can predict the long-term clinical endpoint. An example is the use of progression-free survival as the endpoint in Phase 2 and overall survival in Phase 3 cancer trials.

Occasionally, a sponsor may have to conduct more than one study if the doses chosen in the initial dose-response study are not adequate to estimate the dose-response relationship. This could occur if the doses selected initially are too high (e.g., near the plateau of the dose-response curve) or not low enough. To reduce the chance of having to repeat a dose-response study, Pinheiro (2014) recommends including four to seven doses in a wide dose range (e.g., the ratio of the maximum dose to the minimum dose ≥ 10) in the dose-finding study.

At times, different dose-response studies may need to be conducted for different diseases because a refractory disease may require a higher dose than a milder form of the same disease that has not been previously treated. Similarly, higher doses may be necessary to treat diseases considered to be harder to treat than diseases more responsive to treatments.

1.2.3 Phase 3

If the NME meets the efficacy requirement and passes the initial benefit-risk assessment, it will be further tested to confirm its efficacy. This is the final stage of clinical testing before an application is filed with regulatory agencies for approval. By this time, a commercial formulation of the NME should be available so the final testing could be conducted with the intended formulation. In the rare cases when the commercial formulation differs from the formulation used in Phase 3, a PK study will be required to show that the new formulation is bioequivalent to the previous formulation in important PK properties. For convenience, we will refer to the NME as a drug candidate (or simply a drug) from this phase on.

The US FDA generally requires two well-controlled trials to confirm a drug's effect for a target disease. This means two independent Phase 3 trials or, in some cases, a Phase 3 trial plus a well-conducted high-quality Phase 2 dose-ranging study. The primary reason for requiring two "confirmatory" trials is to ensure that a beneficial result could be replicated.

There are situations, however, when one large well-controlled Phase 3 trial is considered adequate to support marketing approval. This occurs when the first study yields highly persuasive and robust results on a clinical endpoint (e.g., mortality and serious morbidity), and it is deemed unethical by the medical community to repeat a similar study. Here, robust results mean low *P*-values (described in Chap. 2) for the primary (clinical) and key secondary endpoints, consistent results across multiple subgroups, and few issues associated with the conduct of the studies. Interested readers should consult with the FDA guidance (FDA 1998) on providing clinical evidence of effectiveness for human drug and biological products.

Compared with previous phases, Phase 3 enrolls a greater number of patients who are more heterogeneous in their demographic and baseline disease status. Currently, nearly all Phase 3 studies are conducted in multiple countries and in multiple geographic regions. It is at this stage that the majority of premarketing safety data are collected. Since a major objective of Phase 3 trials is to confirm a drug's effect, analyses focus on testing prespecified hypotheses with adequate control for the chance of making a false-positive decision. Operations at this stage require carefully protecting a trial's integrity so that trial results could be trusted. The number of patients included at this stage typically ranges between 1000 and 5000. More patients will be needed if the drug is developed for multiple disorders simultaneously. An example for multiple indications is the development of antibiotics for multiple infections.

Drugs designed to reduce the risk of a clinical endpoint may require thousands, if not tens of thousands of patients. On the other hand, drugs for orphan diseases will enroll many fewer patients. An orphan disease in the United States is defined as a condition that affects fewer than 200,000 people nationwide. Orphan diseases

include well-known diseases such as cystic fibrosis and Lou Gehrig's disease (also called amyotrophic lateral sclerosis, or ALS) and less well-known rare diseases such as Duchenne muscular dystrophy (DMD). DMD affects 1 in 3600 boys.

After a drug's effect is confirmed and benefit-risk assessment supports its use in the target population, the manufacturer will file a marketing application with regulatory agencies, typically in multiple countries. Nearly all applications are for the adult population initially. If the drug is likely to be used in the pediatric population, a manufacturer often has an ongoing pediatric development program or has a plan to initiate pediatric trials at the time of the initial marketing application. The initial marketing application may be for a single indication or for multiple indications. Once the application is approved, the drug can be made available to the public.

As explained earlier, Phase 3 is the time when the majority of safety data are collected. Safety data are crucial for sound benefit-risk assessment. The International Council for Harmonisation describes the extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions (ICH-E1 1994). For these conditions, ICH E1 expects 1500 individuals be exposed to the drug during the clinical development program. Among the 1500 individuals, 100 patients should have been exposed to the drug for at least 1 year. The exposure should be at the dose levels to be marketed. So, for a new drug with a large treatment effect, the need for a reasonable safety database will likely drive the sample size decisions for confirmatory trials.

1.2.4 Phase 4

The manufacturer of a marketed drug may choose to conduct additional studies to further (1) investigate the drug in the indicated population(s) or in pediatric patients with the indicated disorder(s), (2) compare the drug head to head with an approved drug for the same disorder(s), (3) investigate the effect of the drug at a lower/higher dose or with different administration schedules (e.g., once a day instead of twice a day), (4) study the drug in combination with other drugs, or (5) test the drug for other indications. Sometimes, a manufacturer conducts Phase 4 studies as a postmarketing commitment for regulatory approval. For example, the manufacture may be asked to conduct additional safety studies in vulnerable populations such as elderly, pediatric, obese, and pregnant patients.

Another way to characterize the four phases of drug development is by the type of studies conducted during these 4 phases (see ICH E8 1997). The types of studies conducted can be described as human pharmacology studies (Phase 1), therapeutic exploratory studies (Phase 2), therapeutic confirmatory studies (Phase 3), and therapeutic use studies (Phase 4).

1.3 Regulatory Review

Section 1.2 describes a traditional clinical development process. It usually takes many years for an NME to go through the first three phases. Once a marketing application is submitted, the manufacturer waits for the outcome of the regulatory review. Regulators often send queries to the manufacturer during this period for clarification or additional analyses.

In the United States, the FDA often arranges advisory committee meetings to publicly discuss submissions of NMEs or submissions that include unusual or controversial findings. Advisory committees will offer their recommendations to the agency. While these recommendations are not binding, the FDA often chooses to follow them. Before the turn of this century, the waiting period for a regulatory decision in the United States could be substantial. The review time has been significantly reduced since the beginning of the twenty-first century.

In Sects. 1.3.1 through 1.3.5, we will discuss deviations from the traditional review process that can help bring a drug with a clinically meaningful effect on serious conditions to the market faster in the United States.

In Sect. 1.3.6, we will review briefly procedures for drug approvals in the European Union (EU).

1.3.1 Accelerated Approval

In 1992 the FDA instituted the *accelerated approval* regulations, allowing drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint. A surrogate endpoint in this context is a measure of effect that may correlate with a real clinical endpoint but does not necessarily have a guaranteed relationship with the clinical endpoint.

Under the accelerated approval regulations, adequate and well-controlled studies that demonstrate a drug's effect on a surrogate or intermediate clinical endpoint could provide the necessary evidence for the initial marketing approval. This is the path for most cancer drug approvals in the past two decades. Even though the ultimate goal of a cancer treatment is to prolong survival, the initial approval of a cancer drug has been tumor shrinkage. The effect on tumor shrinkage is typically studied in Phase 2 trials. Some of these Phase 2 studies include only patients receiving the NME (i.e., a single arm) and rely on historical data to determine if the NME has a beneficial effect on tumor shrinkage.

With an accelerated approval, the manufacturer of a new NME for cancer still needs to conduct studies to confirm the ability of the drug to prolong survival. For this reason, accelerated approval is sometimes called *conditional* approval since there is a condition associated with the approval. A common industry practice is to

start the clinical endpoint study once the effect of the NME on tumor shrinkage is confirmed. Safety data from the ongoing clinical endpoint study can be used to help augment the safety database to assist regulatory review. The use of interim safety data in this fashion requires special care to protect the integrity of the clinical endpoint study.

Once a confirmatory trial verifies the clinical benefit, the FDA will generally remove the requirement. If the confirmatory trials fail to demonstrate a clinical benefit, the accelerated approval may be withdrawn. A manufacturer often has a chance to conduct multiple studies to confirm the clinical benefit before the agency takes the step to withdraw the approved indication. Even if the approval is allowed to remain for the indication, the product label will be modified to clarify that trials failed to verify clinical benefit.

1.3.2 Breakthrough Therapy

In July 2012, the US Congress signed the FDA Safety and Innovation Act. The Act allows FDA to designate a drug as breakthrough therapy if (1) the drug, used alone or in combination with other drugs, is intended to treat a serious or life-threatening disease or condition and (2) preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on at least one clinically significant endpoint. A manufacturer can submit a request to the FDA to designate a drug as breakthrough therapy. The agency has 60 days to grant or deny the request. The submission should be done prior to the meeting with the agency to review Phase 2 results.

The breakthrough therapy designation allows the manufacturer to receive intensive guidance from the agency on the drug development program. It also signals the agency's commitment to the drug program at the senior management level including an expedited review of the drug's marketing application.

Having a drug designated as a breakthrough therapy is highly desirable. In addition to a quicker agency's response to requests for feedback and a faster review timeline, a breakthrough designation increases the prestige of a drug. A requirement for a breakthrough therapy is preliminary clinical evidence of substantial improvement over existing therapies on at least one clinically meaningful endpoint. The preliminary clinical evidence could come from an early trial in a small number of subjects. Pereira et al. (2012) reported findings from an empirical investigation on how often very large treatment effects were replicated in subsequent trials of the same comparison, disease, and outcome. They concluded that most large treatment effects observed in small studies became much smaller when additional trials were performed. This is a point that we will return to in later chapters of this book (see Chap. 12).

1.3.3 Priority Review

In the United States, the Prescription Drug User Act (PDUFA) came into effect in 1992. Under the Act, manufacturers of prescription drugs pay a fee when submitting an application to market the drugs. In return, the FDA agreed to improve the drug review time with specific goals. The FDA also created a two-tiered review system timeline—*standard review* and *priority review*. The Act is renewable every 5 years. The 2002 amendments to PDUFA (second renewal) set a goal that a standard review of a new drug application be accomplished within 10 months and a priority review be completed within 6 months.

A priority review designation is granted to drugs that, if approved, would contribute significantly to the treatment, diagnosis, or prevention of serious conditions.

In the United States, a priority review voucher is awarded to any company that has obtained approval for a treatment for a neglected tropical disease. The voucher, allowed under a provision of the Food and Drug Administration Amendments Act (H.R. 2007), is intended as an incentive to encourage companies investing in new drugs and vaccines for neglected tropical diseases. The voucher is transferrable.

The awarding of a priority review voucher has created an interesting phenomenon in the United States, that is, the selling of the voucher by its holder to the highest bidder in the open market. In some cases, the price paid for a voucher is hundreds of millions of US dollars. The purchaser can use the voucher toward any drug under regulatory review, hoping to get the drug to the market 6 months earlier or ahead of a rival drug that is being reviewed for the same indication contemporarily.

1.3.4 Fast Track

Another designation that a manufacture could seek of the FDA for their drug is *fast track*. A manufacturer could initiate the request at any time during the development process. The FDA will review the request and make a decision within 60 days based on whether the drug fills an unmet medical need in a serious condition.

A drug receiving the fast-track designation can expect to enjoy more frequent and timely interactions with the FDA. The manufacturer of a fast-track drug can submit sections of the new drug application for the agency review as they are being completed (rolling submission). A fast-tracked drug is eligible for accelerated approval and priority review, if other criteria described earlier are met. Because of more frequent communications and faster resolutions of issues, a fast-track designation often leads to earlier drug approval and access.

1.3.5 Orphan Drug

The US Congress passed the Orphan Drug Act in 1983 to provide incentives for developing treatments for orphan diseases (Kesselheim 2010). The incentives include (1) a federal funding of grants and contracts to perform clinical trials of orphan products, (2) a tax credit of 50% of clinical testing costs, (3) an exclusive right to market the orphan drug for 7 years from the date of marketing approval, (4) a priority review by the FDA, and (5) a waiver of the drug application fees.

Within the class of orphan drugs, the amount of data submitted to support regulatory approval varies greatly. For example, on October 23, 2015, the FDA approved Strensiq (asfotase alfa) as the first treatment for perinatal, infantile, and juvenile-onset hypophosphatasia (FDA Communication 2015). Asfotase alfa, administered via injection three or six times a week, works by replacing the enzyme responsible for forming an essential mineral in the normal bone. The latter has been shown to improve patient overall clinical outcomes.

The approval was based on results from 99 patients who received asfotase alfa treatment for up to 6.5 years in four prospective, nonrandomized studies. Study results showed that patients with the target condition and treated with asfotase alfa had improved overall survival compared with control patients selected from a natural history study group.

1.3.6 Drug Approval in the European Union (EU)

The first EU legislation on human medicine, triggered by the thalidomide catastrophe and adopted in 1965, was Council Directive 65/65 on the approximation of the law relating to medicinal products. This was followed by two council directives in 1975. The first was on approximation of the laws of member states relating to analytical, pharmacotoxicological, and clinical standards and protocols with respect to the testing of proprietary medicinal products. The second was on the approximation of provisions laid down by law, regulation, and administrative action relating to medicinal products. The latter directive established a Committee on Proprietary Medicinal Products as an advisory committee and introduced the procedure now known as the mutual recognition procedure (Rägo and Santoso 2008). A further directive introduced the procedure known today as the centralized procedure. In 1995 the European Medicines Agency was founded to harmonize the work of existing national medicine regulatory bodies and to protect public and animal health by assessing medicines to rigorous standards and providing partners and stakeholders with independent, science-based information on medicines (EMA: History of EMA 2015).