CHAPTER 1

Pharmacometrics: Impacting Drug Development and Pharmacotherapy

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1.1 INTRODUCTION

Drug development continues to be expensive, time consuming, and inefficient, while pharmacotherapy is often practiced at suboptimal levels of performance (1–3). This trend has not waned despite the fact that massive amounts of drug data are obtained each year. Within these massive amounts of data, knowledge that would improve drug development and pharmacotherapy lays hidden and undiscovered. The application of pharmacometric (PM) principles and models to drug development and pharmacotherapy will significantly improve both (4, 5). Furthermore, with drug utilization review, generic competition, managed care organization bidding, and therapeutic substitution, there is increasing pressure for the drug development industry to deliver high-value therapeutic agents.

The Food and Drug Administration (FDA) has expressed its concern about the rising cost and stagnation of drug development in the white paper *Challenge and Opportunity on the Critical Path to New Products* published in March of 2004 (3). In this document the FDA states: "Not enough applied scientific work has been done to create new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated in faster time frames, with more certainty, and at lower costs. . . . A new product development toolkit—containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques—is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product. We need superior product development science to address these challenges." In the critical path document, the FDA states that the three main areas of the path that need to be addressed are tools for assessing safety, tools for demonstrating medical utility, and lastly tools for characterization and manufacturing. Pharmacometrics can be applied to and can impact the first two areas, thus positively impacting the critical path.

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For impacting safety, the FDA has noted opportunities to better define the importance of the QT interval, for improved extrapolation of in vitro and animal data to humans, and for use of extant clinical data to help construct models to screen candidates early in drug development (e.g., liver toxicity). Pharmacometrics can have a role in developing better links for all of these models.

For demonstrating medical utility, the FDA has highlighted the importance of model-based drug development in which pharmacostatistical models of drug efficacy and safety are developed from preclinical and available clinical data. The FDA goes on to say that "Systematic application of this concept to drug development has the potential to significantly improve it. FDA scientists use and are collaborating with others in the refinement of quantitative clinical trial modeling using simulation software to improve trial design and to predict outcomes." The pivotal role of pharmacometrics on the critical path is obvious.

Drug development could be improved by planning to develop and apply PM models along with novel pathways to approval, improved project management, and improved program development. Recent advances in computational speed, novel models, stochastic simulation methods, real-time data collection, and novel biomarkers all portend improvements in drug development.

Dosing strategy and patient selection continue to be the most easily manipulated parts of a patient's therapy. Optimal dosing often depends on patient size, sex, and renal function or liver function. All too often, the impact of these covariates on a PM parameter is unstudied and therefore cannot be incorporated into any therapeutic strategy. PM model development and application will improve both drug development and support rational pharmacotherapy.

1.2 PHARMACOMETRICS DEFINED

Pharmacometrics is the science of developing and applying mathematical and statistical methods to characterize, understand, and predict a drug's pharmacokinetic, pharmacodynamic, and biomarker–outcomes behavior (6). Pharmacometrics lives at the intersection of pharmacokinetic (PK) models, pharmacodynamic (PD) models, pharmacodynamic-biomarker–outcomes link models, data visualization (often by employing informative modern graphical methods), statistics, stochastic simulation, and computer programming. Through pharmacometrics one can quantify the uncertainty of information about model behavior and rationalize knowledge-driven decision making in the drug development process. Pharmacometrics is dependent on knowledge discovery, the application of informative graphics, understanding of biomarkers/surrogate endpoints, and knowledge creation (7–10). When applied to drug development, pharmacometrics often involves the development or estimation of pharmacokinetic, pharmacodynamic, pharmcodynamic–outcomes linking, and disease progression models. These models can be linked and applied to competing study designs to aid in understanding the impact of varying dosing strategies, patient selection criteria, differing statistical methods, and different study endpoints. In the realm of pharmacotherapy, pharmacometrics can be employed to customize patient drug therapy through therapeutic drug monitoring and improved population dosing strategies. To contextualize the role of pharmacometrics in drug development and pharmacotherapy, it is important to examine

the history of pharmacometrics. The growth of pharmacometrics informs much on its content and utility.

1.3 HISTORY OF PHARMACOMETRICS

1.3.1 Pharmacokinetics

Pharmacometrics begins with pharmacokinetics. As far back as 1847, Buchanan understood that the brain content of anesthetics determined the depth of narcosis and depended on the arterial concentration, which in turn was related to the strength of the inhaled mixture (11). Interestingly, Buchanan pointed out that rate of recovery was related to the distribution of ether in the body. Though there was pharmacokinetic (PK) work done earlier, the term pharmacokinetics was first introduced by F. H. Dost in 1953 in his text, *Der Blutspeigel-Kinetic der Knozentrationsablaufe in der Kreislauffussigkeit* (12). The first use in the English language occurred in 1961 when Nelson published his "Kinetics of Drug Absorption, Distribution, Metabolism, and Excretion" (13). The exact word pharmacokinetics was not used in this publication.

In their classic work, the German scientists Michaelis and Menton published their equation describing enzyme kinetics in 1913 (14). This equation is still used today to describe the kinetics of drugs such as phenytoin. Widmark and Tandberg (15) published the equations for the one-compartment model in 1924 and in that same year Haggard (16) published his work on the uptake, distribution, and elimination of diethyl ether. In 1934 Dominguez and Pomerene (17) introduced the concept of volume of distribution, which was defined as "the hypothetical volume of body fluid dissolving the substance at the same concentration as the plasma. In 1937 Teorrel (18) published a seminal paper that is now considered the foundation of modern pharmacokinetics. This paper was the first physiologically based PK model, which included a five-compartment model. Bioavailability was introduced as a term in 1945 by Oser and colleagues (19), while Lapp (20) in France was working on excretions kinetics.

Polyexponential curve fitting was introduced by Perl in 1960 (21). The use of analog computers for curve fitting and simulation was introduced in 1960 by two groups of researchers (22, 23).

The great growth period for pharmacokinetics was from 1961 to 1972, starting with the landmark works of Wagner and Nelson (24). In 1962 the first symposium with the title pharmacokinetics, "Pharmacokinetik und Arzniemitteldosireung," was held.

Clinical pharmacokinetics began to be recognized in the 1970s, especially in two papers by Gibaldi and Levy, "Pharmacokinetics in Clinical Practice," in the *Journal of the American Medical Association* in 1976 (25). Of further importance that same year was a paper by Koup et al. (26) on a system for the monitoring and dosing of theophylline based on pharmacokinetic principles.

Rational drug therapy is based on the assumption of a causal relationship between exposure and response. There pharmacokinetics has great utility when linked to pharmacodynamics and the examination of pharmacodynamics is of paramount importance.

1.3.2 Pharmacodynamics

In 1848 Dungilson (27) stated that pharmacodynamics was "a division of pharmacology which considers the effects and uses of medicines." This definition has been refined and restricted over the centuries to a more useful definition, where "pharmacokinetics is what the body does to the drug; pharmacodynamics is what the drug does to the body" (28, 29). More specifically, pharmacodynamics was best defined by Derendorf et al. (28) as "a broad term that is intended to include all of the pharmacological actions, pathophysiological effects and therapeutic responses both beneficial or adverse of active drug ingredient, therapeutic moiety, and/or its metabolite(s) on various systems of the body from subcellular effects to clinical outcomes." Pharmacodynamics most often involves mathematical models, which relate some concentration (serum, blood, urine) to a physiologic effect (blood pressure, liver function tests) and clinical outcome (survival, adverse effect). The pharmacodynamic (PD) models have been described as fixed, linear, log-linear, E_{max}, sigmoid E_{max}, and indirect PD response (29–31).

The indirect PD response model has been a particularly significant contribution to PD modeling (30, 31). It has great utility because it is more mechanistic than the other models, does not assume symmetry of the onset and offset, and incorporates the impact of time in addition to drug concentration, thus accounting for a delay in onset and offset of the effect. For these models the maximum response occurs later than the time of occurrence of the maximum plasma concentration because the drug causes incremental inhibition or stimulation as long as the concentration is "high enough." After the response reaches the maximum, the return to baseline is a function of the dynamic model parameters and drug elimination. Thus, there is a response that lasts beyond the presence of effective drug levels because of the time needed for the system to regain equilibrium. Whenever possible, these mechanistic models should be employed for PD modeling and several dose levels should be employed for accurate determination of the PD parameters, taking into consideration the resolution in exposure between doses.

The dependent variables in these PD models are either biomarkers, surrogate endpoints, or clinical endpoints. It is important to differentiate between these and to understand their relative importance and utility.

1.3.3 Biomarkers

The importance of biomarkers has been noted in recent years and is evidenced by the formation of The Biomarkers Definitions Working Group (BDWG) (32). According to the BDWG, a biomarker is a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic process or pharmacologic responses to a therapeutic intervention." Biomarkers cannot serve as penultimate clinical endpoints in confirming clinical trials; however, there is usually considered to be some link between a biomarker based on prior therapeutic experience, well understood physiology or pathophysiology, along with knowledge of the drug mechanism. Biomarkers often have the advantage of changing in drug therapy prior to the clinical endpoint that will ultimately be employed to determine drug effect, thus providing evidence early in clinical drug development of potential efficacy or safety.

A surrogate endpoint is "a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit, harm, lack of benefit, or lack of harm based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence" (32). Surrogate endpoints are a subset of biomarkers such as viral load or blood pressure. All surrogate endpoints are biomarkers. However, few biomarkers will ever become surrogate endpoints. Biomarkers are reclassified as surrogate endpoints when a preponderance of evidence indicates that changes in the biomarker correlate strongly with the desired clinical endpoint.

A clinical endpoint is "a characteristic or variable that reflects how a patient feels, functions or survives. It is a distinct measurement or analysis of disease characteristics observed in a study or a clinical trial that reflect the effect of a therapeutic intervention. Clinical endpoints are the most credible characteristics used in the assessment of the benefits and risks of a therapeutic intervention in randomized clinical trials." There can be problems with using clinical endpoints as the final measure of patient response because a large patient sample size may be needed to determine drug effect or the modification in the clinical endpoint for a drug may not be detectable for several years after the initiation of therapy.

There are several ways in which the discovery and utilization of biomarkers can provide insight into the drug development process and patient care. Biomarkers can identify patients at risk for a disease, predict patient response, predict the occurrence of toxicity, and predict exposure to the drug. Given these uses, biomarkers can also provide a basis for selecting lead compounds for development and can contribute knowledge about clinical pharmacology. Therefore, biomarkers have the potential to be one of the pivotal factors in drug development—from drug target discovery through preclinical development to clinical development to regulatory approval and labeling information, by way of pharmacokinetic/pharmacodynamic–outcomes modeling with clinical trial simulations.

1.3.4 PK/PD Link Modeling

PK/PD modeling provides the seamless integration of PK and PD models to arrive at an enlightened understanding of the dose–exposure–response relationship. PK/PD modeling can be done either sequentially or simultaneously (33, 34). Sequential models estimate the pharmacokinetics first and fix the PK parameters, generating concentrations corresponding to some PD measurement. Thus, the pharmacodynamics is conditioned on the PK data or on the estimates of the PK parameters. Simultaneous PK/PD modeling fits all the PK and PD data at once and the PK and PD parameters are considered to be jointly distributed. When simultaneous modeling is done, the flow of information is bidirectional. Both of these approaches appear to provide similar results (33, 35). However, it is important to note that PD measurements are usually less precise than PK measurements and using sequential PK and PD modeling may be the preferred approach in most instances.

PK and PD can be linked directly through a measured concentration that is directly linked to an effect site. The direct link model does not work well when there is a temporal relationship between a measured concentration and effect, as when hysteresis is present. When this is the case, an indirect link between the measured concentration and effect must be accounted for in the model. This has been done in

general by the construction of an effect compartment, where a hypothetical effect compartment is linked to a PK compartment. Here the effect compartment is very small and thus has negligible impact on mass balance with a concentration time course in the effect compartment. The effect is related to the concentration in the effect compartment, which has a different time course than the compartment where drug concentrations are actually measured. In addition to the effect compartment approach to account for temporal concentration–effect relationships, the indirect response concept has found great utility.

PK and PD have been linked by many models, sometimes mechanistic and at other times empirical. These models are especially useful in better understanding the dose strategy and response, especially when applied by stochastic simulation. The population approach can be applied to multiple types of data—for example, both intensely and sparsely sampled data and preclinical to Phase 4 clinical data—and therefore has found great utility when applied to PK/PD modeling.

1.3.5 Emergence of Pharmacometrics

The term pharmacometrics first appeared in the literature in 1982 in the *Journal of Pharmacokinetics and Biopharmaceutics* (36). At that time, the journal made a commitment to a regular column dealing with the emerging discipline of pharmacometrics, which was defined as "the design, modeling, and analysis of experiments involving complex dynamic systems in the field of pharmacokinetics and biopharmaceutics . . . concerning primarily data analysis problems with such models." They went on to say that problems with study design, determination of model identifiability, estimation, and hypothesis testing would be addressed along with identifying the importance of graphical methods. Since this time, the importance of pharmacometrics in optimizing pharmacotherapy and drug development has been recognized, and several graduate programs have been established that emphasize pharmacometrics (37). Pharmacometrics is therefore the science of developing and applying mathematical and statistical methods to (a) characterize, understand, and predict a drug's pharmacokinetic and pharmacodynamic behavior; (b) quantify uncertainty of information about that behavior; and (c) rationalize data-driven decision making in the drug development process and pharmacotherapy. In effect, pharmacometrics is the science of quantitative pharmacology.

1.3.6 Population Modeling

A major development in pharmacometrics was the application of population methods to the estimation of PM parameters (38). With the advent of population approaches, one could now obtain estimates of PM parameters from sparse data from large databases and also obtain improved estimates of the random effects (variances) in the parameters of interest. These models first found great applicability by taking massive amounts of data obtained during therapeutic drug monitoring (TDM) from which typical values and variability of PK parameters were obtained. The parameters once estimated were applied to TDM to estimate initial doses and, using Bayesian algorithms, to estimate a patient's individual PK parameters to optimize dosing strategies. Population methods have become widely accepted to the

extent that a *Guidance for Industry* has been issued by the United States Food and Drug Administration (FDA) on population pharmacokinetics. Population methods are applied to pharmacokinetics, pharmacodynamics, and models linking biomarkers to clinical outcomes (39).

1.3.7 Stochastic Simulation

Stochastic simulation was another step forward in the arena of pharmacometrics. Simulation had been widely used in the aerospace industry, engineering, and econometrics prior to its application in pharmacometrics. Simulation of clinical trials first appeared in the clinical pharmacology literature in 1971 (40) but has only recently gained momentum as a useful tool for examining the power, efficiency, robustness, and informativeness of complex clinical trial structure (41).

A major impetus promoting the use of clinical trial simulation was presented in a publication by Hale et al. (41), who demonstrated the utility of simulating a clinical trial on the construction of a pivotal study targeting regulatory approval. The FDA has shown interest in clinical trial simulation to the extent that it has said: "Simulation is a useful tool to provide convincing objective evidence of the merits of a proposed study design and analysis. Simulating a planned study offers a potentially useful tool for evaluating and understanding the consequences of different study designs" (39). While we often think of clinical trial simulation as a way for the drug sponsor to determine optimal study structure, it is also a way for the FDA to determine the acceptability of a proposed study protocol. Simulation serves as a tool not only to evaluate the value of a study structure but also to communicate the logical implications of a PM model, such as the logical implication of competing dosing strategies for labeling.

The use and role of a simulated Phase 3 safety and efficacy study is still under discussion as confirmatory evidence at the FDA; however, a simulation of this type can serve as supportive evidence for regulatory review (4, 5). It is likely that at some time in the future knowledge of a disease's pathophysiology plus knowledge of drug behavior and action will be applied to a group of virtual patients as the pivotal Phase 3 study for approval by a clinical trial simulation. Stochastic simulation should result in more powerful, efficient, robust, and informative clinical trials; therefore, more can be learned, and confirming efficacy will be more certain as stochastic simulation is applied to the drug development process.

1.3.8 Learn–Confirm–Learn Process

Drug development has traditionally been empirical and proceeded sequentially from preclinical through clinical Phases 1 to 3. Sheiner (42) first proposed a major paradigm shift in drug development away from an empirical approach to the learn–confirm approach based on Box's inductive versus deductive cycles (43). Williams et al. (6, 44) and Ette et al. (45) have since revised this process to the learn–confirm–learn approach because of their emphasis on the fact that learning continues throughout the entire drug development process. The learn–confirm–learn process contends that drug development ought to consist of alternate cycles of learning from experience and then confirming what has been learned but that one never proposes a protocol where learning ceases.

In the past, Phases 1 and 2a have been considered the learning phases of drug development because the primary objectives are to determine the tolerated doses and the doses producing the desired therapeutic effect. Phase 2 has targeted how to use the drug in the target patient population, determining the dose strategy and proof of concept. Phase 3 has focused on confirming efficacy and demonstrating a low incidence of adverse events, where if the ratio of benefit to risk is acceptable then the drug is approved. An encouraging outcome in these early cycles results in investment in the costly Phase 2b and 3 studies. However, even in the confirming stages of drug development, one ought to continue to be interested in learning even though confirming is the primary objective of a study; that is, all studies should incorporate an opportunity for learning in the protocol. Therefore, the process has been renamed "learn–confirm–learn".

Learning and confirming have quite different goals in the process of drug development. When a trial structure optimizes confirming, it most often imposes some restrictions on learning; for example, patient enrollment criteria are limited, thus limiting one's ability to learn about the agent in a variety of populations. For example, many protocols limit enrollment to patients with creatinine clearances above a certain number (e.g., 50 mL/min). If this is done, one cannot learn how to use such a drug in patients with compromised renal function. Empirical commercial drug development has in general focused on confirming because it provides the necessary knowledge for regulatory approval, addressing the primary issue of efficacy. The downside of the focus on confirming is that it has led to a lack of learning, which can result in a dysfunctional drug development process and less than optimal pharmacotherapy postapproval.

PM modeling focuses on learning, where the focus is on building a model that relates dosing strategy, exposure, patient type, prognostic variables, and more to outcomes. Here the three-dimensional response surface is built (42) (see Section 1.3.9.2). PM models are built to define the response surface to increase the signal-to-noise ratio, which will be discussed shortly. The entire drug development process is an exercise of the learn–confirm–learn paradigm.

1.3.9 Exposure–Response Relationship

The importance of elucidating the exposure–response relationship must be emphasized. When the term exposure is used, one is usually referring to dose or variables related to concentration such as area under the concentration–time curve (AUC), maximum concentration (C_{max}), minimum concentration (C_{min}), or average concentration (C_{ave}) in some biological specimen such as serum, urine, cerebral spinal fluid, or sputum. It is worth noting that dose is a very weak surrogate of exposure, especially where there is no proportionality between dose and AUC or C_{max}. Response is a measure of the effect of a drug either therapeutic or adverse, such as blood pressure, cardiac index, blood sugar, survival, liver function, or renal function.

1.3.9.1 Regulatory Perspective

The FDA document, *Guidance for Industry: Exposure–Response Relationships—Study Design, Data Analysis, and Regulatory Applications*, has commented extensively on the exposure–response relationship (46). It states: "Exposure–response information is at the heart of any determination of the safety and effectiveness of

drugs. . . . In most cases, however, it is important to develop information on the population exposure–response relationships for favorable and unfavorable effects and information on how, and whether, exposure can be adjusted for various subsets of the population." The FDA recognizes the value of exposure–response knowledge to support the drug development process and to support the determination of safety and efficacy. In this document it stated that "dose–response studies can, in some cases, be particularly convincing and can include elements of consistency that, depending on the size of the study and outcome, can allow reliance on a single clinical efficacy study as evidence of effectiveness." The exposure–response relationship was further refined in the defining of the response surface.

1.3.9.2 Response Surface

A significant development of the exposure–response concept was the proposing of the response surface. Sheiner (42) first proposed the pharmacological response surface as a philosophical framework for development of PM models. The response surface can be thought of as three dimensional: on one axis are the input variables (dose, concurrent therapies, etc.); on the second axis are the important ways that patients can differ from one another that affect the benefit to toxicity ratio; and the final axis represents the benefit to toxicity ratio. Sheiner stated: "the real surface is neither static, nor is all the information about the patient conveyed by his/her initial prognostic status, nor are exact predictions possible. A realistically useful response . . . must include the elements of variability, uncertainty and time . . ." Thus, the primary goal of the response model is to define the complex relationship between the input profile and dose magnitude when comparing beneficial and harmful pharmacological effects and how this relationship varies between patients. For rational drug use and drug development, the response surface must be mapped. PM models, once developed and validated, allow extrapolation beyond the immediate study subjects to allow application to other patients from whom the model was not derived. These predictive models permit the evaluation of outcomes of competing dosing strategies in patients who have not received the drug and therefore aid in constructing future pivotal studies. One important aspect of PM models employed in mapping the response surface is that they increase the signal-to-noise ratio in a data set because they translate some of the noise into signal. This is important because when we are converting information (data) into knowledge, the knowledge is proportional to the signal-to-noise ratio.

1.3.10 PM Knowledge Discovery

It is our experience that most drug development programs are data rich and knowledge poor. This occurs when data are collected but all of the knowledge hidden in the data set is not extracted. In reality, huge amounts of data are generated from modern clinical trials, observational studies, and clinical practice, but at the same time there is an acute widening gap between data collection, knowledge, and comprehension. PM knowledge discovery applies 13 comprehensive and interwoven steps to PM model development and communication and relies heavily on modern statistical techniques, modern informative graphical applications, and population modeling (8, 9) (see Chapter 14). The more that is known about a drug the better will be its application to direct patient care, and the more powerful and efficient

will be the development program. To this end, PM knowledge discovery is the best approach to extracting knowledge from data and has been defined and applied to PM model development.

1.3.11 PM Knowledge Creation

Most often, knowledge discovery provides the foundation for knowledge creation and is simply the initial step in the application of PM knowledge (10). The discovered knowledge can be used to synthesize new data or knowledge, or to supplement existing data. PM knowledge creation has something in common with knowledge discovery its intent to understand and better define the response surface. Data supplementation deals with the use of models on available data to generate supplemental data that would be used to characterize a targeted unexplored segment of the response surface (47).

1.3.12 Model Appropriateness

Model appropriateness brought a new epistemology to PM model estimation and development (48) (see Chapter 8). The pivotal event in establishing model appropriateness is stating the intended use of the model. The entire process requires the stating of the intended use of the model, classifying the model as either descriptive or predictive, evaluating the model, and validating the model if the model is to be used for predictive purposes. Descriptive models are not intended to be applied to any external population—that is, their sole purpose is to gain knowledge about the drug in the population studied. Predictive models are intended to be applied to subjects from whom the model was not derived or estimated. Predictive models require a higher degree of correspondence to the external universe than descriptive models and therefore require validation.

Under the epistemology of model appropriateness, the purpose for which the model is developed has a significant impact on the modeling process. In the current modeling climate, insufficient consideration is given to the purpose or intended use of the model and little attention is given to whether the model is descriptive or predictive. Model appropriateness is a paradigm that ought to be applied to the model development and estimation process and it provides the framework for appropriate use of PM models.

1.4 PIVOTAL ROLE OF PHARMACOMETRICS IN DRUG DEVELOPMENT

Drug development has become protracted and expensive over the last several decades, with the average length of clinical development being over 7–12 years, the number of studies averaging 66, and a cost of $0.802–1.7 billion per approved agent (1–4). The process has been empirical—driven by identifying all the items needed for registration of an agent, constructing a checkbox for each item, and executing the studies so that each box is checked, with a consequent fulfillment of each requirement. The numbers above indicate that this empirical, “it has always been done this way” approach does not work well and novel approaches need to be applied. The learn–confirm–learn paradigm should be applied to all drug

development programs, and modeling should follow the epistemology of model appropriateness.

To expedite drug development while maintaining patient safety, new technologies and approaches to discovery, improved project and development approaches, portfolio review, application of sound science, novel study structures, and pharmacometrically guided development programs will need to emerge (49). The use of pharmacometrics to define the dose exposure–response relationship has been successful in improving drug development and pharmacotherapy. Of pivotal importance here is the learn–confirm–learn paradigm, which has been previously mentioned as one of the significant proposals in the evolution of pharmacometrics.

While pharmacometrics can be an important tool to expedite drug development, it will also play a key role in determining the optimal dose at the time of approval (new drug application approval). Going to market with the optimal dose is not as straightforward as one may expect. A recent retrospective study noted that of 499 approved drugs between 1980 and 1999, one in five had a dosage change postapproval and 80% of these changes were a decrease in dose (50). This study concluded that current drug development frequently does not capture completely the dose information needed for safe pharmacotherapy. To address this, Cross et al. (50) suggested that improved PK and PD information be gathered early in Phase 2 of drug development. Finally, if drug doses are higher than need be during development and adverse events are related to dose, this may result in an increased frequency of adverse events resulting in an increased study dropout rate and therefore a decrease in study power.

Finding the optimal dose is one of the primary goals of clinical development, because changing a dose based on patient characteristics can easily be done. Simplified dosing strategies are often sought by the drug sponsor because it results in ease of use by the practitioner and the patient. Often a sponsor wants a "one dose fits all" approach, which may not result in optimized dosing. Often several levels of dose stratification result in surprisingly improved dosing strategies (e.g., elderly versus young).

Novel study structures, such as the enrichment trial, fusion, and adaptive design studies, will result in more efficient drug development. Enrichment studies attempt to choose subjects who are likely to respond. Study groups can be "enriched" by enrolling only subjects with response markers in a specific range or by enrolling only subject types demonstrating a good response during a short pretest phase. In enrichment trials the exposure relationship can be studied efficiently, but it is difficult to know how to extrapolate the quantitative relationship (exposure–response) from an enrichment study to the general population.

The advantage of the adaptive design study is that it emphasizes study of the drug in the region of useful doses, thus minimizing the number of subjects in regions where the drug is not effective. For adaptive designs, an exposure–response model is used and continuously updated as each subject's response is observed. The updated model is used to generate the probability of allocation of each new subject to a treatment arm, favoring the allocation to those arms with the better accumulated outcomes to date, with new subjects randomly allocated to arms on the basis of these frequencies. A treatment arm is dropped from the remainder of the study when its allocation probability drops below a specified threshold. The efficiency of this study design is that as few subjects as necessary are studied to determine that

one dose level is less useful than another. This approach can decrease study duration and numbers of subject in a clinical study. Adaptive design works best when patient accrual rates are slow.

1.4.1 Preclinical Development

Drug discovery has focused on identifying the most potent lead compound for a specified target. However, many drugs have failed due to poor pharmacokinetic or biopharmaceutical properties such as a short half-life or poor bioavailability. In today's economic environment such failures can no longer be afforded. It has become recognized that the "best drug" is one that balances potency, good pharmacokinetic–biopharmaceutical properties, good pharmacodynamics, safety, and low cost of manufacturing. It is important to deal with these issues prior to testing in humans.

Optimized preclinical development can be a tremendous aid to the design of early clinical studies. This optimization will include a thorough study of preclinical safety by combining traditional toxicology studies with novel methods in toxicoproteomics, toxicogenomics, and metabolomics. These new "-omics" will lead to novel biomarkers to predict toxicology and efficacy.

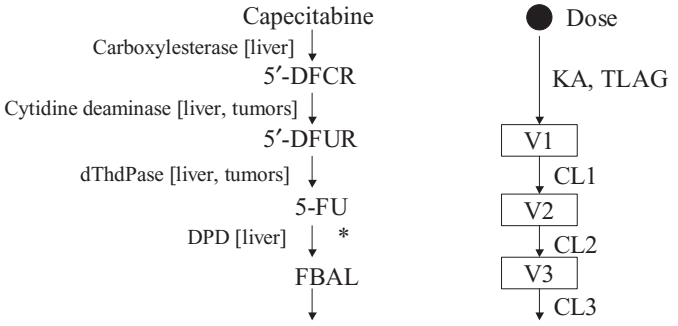
Preclinical development should play an important role in defining the exposure–response (both efficacy and toxicity) relationships, which is a primary role for preclinical pharmacometrics. It is essential to determine the absorption, distribution, metabolism, and elimination during toxicokinetic studies in order to understand the comparison of these across species. It has been demonstrated that by combining preclinical exposure–response data (the steepness of the curve is important here), preclinical pharmacokinetics, and novel approaches to scale up to humans (10, 51) (see also Chapters 29 and 30), Phase 1 can be expedited. This can be done by choosing higher first time in human doses or more rapid escalation (if the dose–response curve is rather flat), resulting in fewer dosing cycles and thus less time, energy, and finances expended on Phase 1, without sacrificing safety.

The development of physiologically and pathophysiologically based PM models (PBPM models) during preclinical development deserves attention. These models have the potential to provide accurate and nearly complete characterization of the PK and concentration–effect relationship and quantification of the potency of a drug (52–56). PBPM testing is best executed when the chemistry, biochemistry, metabolism, and exposure response of the drug are well known in addition to the relative physiology of the animals used in preclinical trials versus the parallel human physiology. To utilize PBPM modeling one must define the physiology, pathophysiology, biochemistry, and exposure–response relationships. To execute this type of modeling, some of the physiological variables that often need to be defined include blood flow to various organs such as liver, kidney, and effect organs. The biochemical–pharmacological parameters of a model that often need to be defined are K_m and $V_{\max}$ for the various enzymes that catalyze the metabolism of the drug and/or metabolites; tissue to blood concentration ratios; the distribution of the drug and/or metabolites of interest, for example, protein binding; and the clearance for various organs, for example, liver versus kidney. Exposure–response variables that are associated with a positive response or an adverse event need to be identified such as area under the concentration–time curve (AUC) or maximum concentra-

tion (C_{max}) or nadir concentration (C_{min}). The exposure response may be related to the parent compound or to a metabolite and may be a concentration-based variable in plasma or within a specific organ or tumor. Many of these parameters can be estimated in vitro, such as enzyme kinetic parameters and protein binding, and physiologic parameters can be obtained from the literature, such as blood flow rates and organ volumes (56).

PBPM modeling enabled the evaluation of the pharmacometrics of capecitabine for determination of the optimal dosing strategy in humans (56). Capecitabine is a prodrug that is converted in three steps to 5-fluorouracil (5-FU). A multicompartmental model was developed to describe the pharmacometrics of capecitabine, two metabolites, and 5-FU. The PBPM model is shown in Figure 1.1. The model included five compartments, all in some way related to either efficacy or adverse event. The parameters included in the model were K_m and V_{max} for each of the enzymes that catalyze capecitabine to 5-FU; tissue to blood ratio of capecitabine and the metabolites in gastrointestinal (GI), liver, and tumor tissue; protein binding; blood flow rate to liver, GI, and tumor tissue; and urinary clearance of unbound capecitabine and its metabolites. Enzyme activities (liver, breast, and colorectal tumors) and protein binding parameters were derived from in vitro experiments. Physiologic parameters were obtained from the literature.

From the model, the 5-FU AUC values in breast and colorectal tumors were simulated at doses from 829 to 1255 mg/m^2. The 5-FU AUC in tumor increased in a nonlinear manner relative to the increases in capecitabine dose. The model indicated that, for capecitabine, the 5-FU exposure in the tumors was much greater than in blood, resulting in a relatively low systemic exposure. The simulated blood



* Intermediate metabolites: FUH_2, FUPA

FIGURE 1.1 Metabolic pathway of capecitabine and its representation by a PK model. Abbreviations: Tissues with high enzyme activites are shown in square brackets; 5′-DFCR = 5′deoxy-5-flurocytidine; 5′-DFUR = 5′deoxy-5-flurouridine; dThdPase = thymidine phosphorylase; DPD = dihydropyrimidine dehydrogenase; FBAL = α-fluoro-β-alanine; FUH_2 = dihydro-5-fluorouracil; FUPA = 5-fluoro-ureido-propionic acid. Dose = capecitabine dose (mg); KA = first-order absorption rate constant (L/h); TLAG = lagtime (h); CL1 = apparent 5′-DFUR clearance (L/h); V1 = apparent 5′-DFUR volume (L); CL2 = apparent 5-FU clearance (L/h); V2 = apparent 5-FU volume (V); CL3 = apparent FBAL clearance (L/h); V3 = apparent FBAL volume (L). (From Blesch et al. (56); used with permission.)

AUC values were consistent with clinical observations, indicating that the model was able to describe known clinical data.

Once the model was developed, a murine xenograft was done and the PK, blood, and tissue binding of capecitabine and its metabolites were measured in vivo and integrated into the PBPM model. Large interspecies differences in tissue distribution and metabolic activity were observed. The predicted blood and tissue concentration profiles of 5-FU in the xenograft were compared to those in humans after simulated oral administration of several levels of capecitabine doses. The 5-FU *AUC*s in blood and xenograft tumor tissues were lower than those in humans for all capecitabine doses administered. At their effective oral doses of capecitabine (0.0944 mmol/kg, the clinical effective dose for humans; 0.44 mmol/kg, the effective dose for human cancer xenograft) similar 5-FU *AUC* values were observed in humans and human cancer xenograft models. The results of this study strongly supported the fact that a clinically effective dose can be extrapolated from xenograft models to a corresponding effect dose in humans when thoughtful approaches to the development and application of PBPM modeling is executed. Preclinical PM modeling should be done on a real-time basis so that modeling has been completed prior to planning and protocol development for Phase 1.

Biomarkers need to be identified and investigated in preclinical studies, especially those that may predict future safety problems. Sometimes the lowering of blood pressure or the prolongation of the corrected QT interval may give one a "heads up" to potential toxicities or dose-related toxicities that may occur during clinical development. When a thorough job is done during preclinical development, then transition to clinical development can be done efficiently and with confidence.

1.4.2 Clinical Development

Clinical development continues with the application of the learn–confirm–learn paradigm applied to drug development. Scale up to the first-time-in-human (FTIH) study is best done by the application of sound PM methods as described by several authors (10, 51, 56).

1.4.2.1 Phase 1 Studies

Phase 1 studies are executed to identify well tolerated doses and, in some cases, the maximum tolerated dose, to study the single and multiple dose pharmacokinetics, and to gain an initial knowledge of the exposure–response relationship. In addition to the above, one sometimes does Phase 1 studies to determine food effect and gender on pharmacokinetics, drug–drug interactions, and pharmacokinetics in special populations such as those with impaired renal or hepatic function or pediatric or geriatric patients. Here one has learned about the dose–exposure–response relationship from preclinical studies, has been guided by that preclinical knowledge, and is confirming or revising what was learned. Both traditional two-stage and population PK methods have been applied to Phase 1 model development with good results. The population approach can provide valuable information that is otherwise not available by the standard two-stage approach. Phase 1 studies are most often conducted in healthy volunteers unless the anticipated toxicity of the drug is severe or the drug is being applied to a life-threatening condition for which no other treatment is available.

In Phase 1, the approach to the FTIH study is critical in determining how much time is expended in this part of development. The central issue here is: "What should the first dose be and how rapidly does escalation occur?" If the very first dose it too high, then an adverse event will occur; if it is too low, then unnecessary time will be expended on low-dose testing. The application of preclinical findings becomes important. A promising approach has been the combining of allometry and mixed effect modeling with stochastic simulation to extrapolate preclinical models and knowledge to humans (10, 51). Applying sound PM methods has been and will be of great value in bringing efficiency to Phase 1 studies and for discovering knowledge that was previously hidden in most Phase 1 data sets. In situations where the maximum tolerated dose (MTD) is sought and defined in healthy volunteers, it should be redefined in patients at some later stage of development if possible (57, 58).

In addition to the FTIH studies, the effects of food, drug–drug interactions, and special populations need to be studied. Coadminstration of drugs has been demonstrated to both increase and decrease bioavailability of some agents with the subsequent lack of efficacy or appearance of toxicity. Further details on the design and conduct of food effect studies can be found in Chapter 29. Drug–drug interaction studies have become increasingly important as the number of agents prescribed to patients continues to increase. In one instance, a prominent drug was withdrawn from the market after adverse events were reported, which were due to interactions with other agents. It is important to obtain information for some subpopulations, such as pediatric patients, those with renal impairment, and the elderly, so that group-specific dosing guidelines can be developed. These special studies can be executed with either traditional PK studies or more efficiently by applying population techniques (39) (see Chapters 12 and 39). The need to study subpopulations strongly supports implementing the learn–confirm–learn paradigm. These issues are addressed in Chapter 14.

As the development process nears the end of Phase 1, it becomes crucial to extract all knowledge from existing data. PM models should be developed, linking drug exposure to pharmacodynamics (response). These models are applied, often by stochastic simulation, to optimize the structure and designs of Phase 2 studies. Real-time data collection is helpful here so that PM models may be estimated prior to data set closure and then applied to evaluation of competing Phase 2a study designs (39, 48, 59, 60). In this way, efficient and powerful Phase 2 programs can be constructed.

1.4.2.2 Phase 2 Studies

Phase 2 studies should focus on both learning and confirming. Historically, Phase 2a has had as its primary goal to demonstrate "proof of concept" that the drug is capable of being effective. It has been a common practice to administer the maximum tolerated dose (MTD) in Phase 2a and this dose may be on the flat part of the efficacy curve. If this is the case, lower doses may have been equally effective and less toxic. This dose is then carried forward into Phase 2b and eventually Phase 3. In Phase 3 the drug will likely be demonstrated to be effective and without significant adverse effects. The result will be NDA approval at the MTD. Therefore, doses may be lowered because "a lower dose is quite adequate for treatment and less expensive" in the opinion of the prescriber or "a lower safer dose may be

needed." The former may be enacted by practitioners without a change in labeling and the latter would come at the directive of the FDA. The former can be quite costly in terms of gross revenues for the manufacturer because an increase in cost per unit after marketing is in general not a viable alternative.

Phase 2a should have learning as its primary focus to define the optimal dose, thus improving the drug development process; while Phase 2b studies should focus on confirming. Phase 2a is the time during development to learn about efficacy; to confirm or modify what was learned in Phase 1 about safety, efficacy, and drug effect on biomarkers; and to refine the dose–PK/PD-biomarkers–surrogate–outcomes relationships.

The knowledge discovered in Phase 2a provides information for the later larger trials that will be designed to prove efficacy. The sample sizes are small in Phase 2 and the patients are often the "healthiest" to minimize disease-related variability. With this in mind, the Phase 2a study should be designed to give a first glimpse to the following issues (48): (a) Does the drug work? (b) How does the drug work? (c) What is the dose–response relationship? (d) Is there a difference in any of the pharmacology in subgroups? A very valuable practice here is to power these studies by setting α at a more liberal level of 0.10–0.20 when evaluating efficacy. Addressing these issues will require paying attention to important design points such as number and level of doses studied, timing of endpoint observations, number of subjects at each dosing level, and duration of the study. Furthermore, a well designed Phase 2a trial with 150–200 subjects will usually provide more information and is less costly than several smaller studies, even when these are later combined (48). A well designed study here will usually depend on stochastic simulation of competing study designs. In the end, many of the analyses will be population dose–pharmacokinetics/pharmacodynamics–response models.

In Phase 2 the proof of concept study provides scientifically sound evidence supporting the postulated effect of the new drug, where the effect may be the relevant pharmacological action or a change in disease biomarkers, established surrogate endpoints, or clinical outcomes that may be beneficial and/or toxic in nature. The proof of concept is often used for go/no-go decisions and is therefore one of the most critical steps in the drug development process.

Biomarkers play an important role in Phase 2 studies. These are covered in Chapter 20 in detail. Biomarkers are most important in early efficacy and toxicity studies when clinical endpoints take too long to become observable. After approval, biomarkers may prove useful in monitoring the course of pharmacotherapy in individual patients.

Prior to advancing to Phase 2b, all the knowledge hidden in the Phase 1 and Phase 2a data ought to be discovered. Then clinical trial simulation (knowledge creation) should be applied to construct Phase 2b.

In Phase 2b the knowledge discovered in all previous phases is confirmed, and learning more about the drug in a larger patient population continues. In this phase of development, strong supportive evidence is generated so that if an accelerated approval is sought the knowledge and data generated could be enough to obviate the need for two Phase 3 confirming studies. Attention should be given to informatively designing Phase 2b studies to meet the confirming study objectives and allow learning that will enhance a further characterization of the response surface. Pharmacokinetics enables the refinement and further development of PK/PD models

for dosage optimization (see Chapter 29). In Phase 2b sparse sampling is adequate; this data may be concatenated with previously collected data. The concatenation of these data with previously collected data and the estimation of individual PK or PD parameters via post hoc Bayesian algorithms may be useful for explaining individual treatment failures, toxicities, or positive responses to a drug. The PM models estimated from all previous data and available at the end of Phase 2b are important for constructing the pivotal Phase 3 program through knowledge creation.

1.4.2.3 Phase 3

Phase 3 is the pivotal phase for registration of a drug, where usually two large randomized, controlled trials for establishing efficacy and safety are required. The PM models from all previous studies are crucial for the determination of the dose(s), patient population selection, study duration, number of patients, and so on for Phase 3. In some cases a single pivotal study may be acceptable to the regulatory agency provided there is good supportive science (which may be good PM models) and confirmatory evidence supporting efficacy and safety (6, 7). In Phase 3 it is still advisable to proceed with sparse collection of PK and PD variables. These data can further support registration, may provide explanations for clinical trial success or failure, and are inexpensive to obtain when compared with the cost of enrolling patients.

1.4.2.4 Phase 4

Phase 4 studies are sometimes required by regulatory agencies. This can happen if the regulatory agency is interested in further characterizing safety, exploring new treatment indications, broadening label claims, exploring new drug combinations, or examining dosing in some special subpopulations (e.g., pediatric patients).

1.5 PHARMACOMETRICS AND REGULATORY AGENCIES

The FDA has promoted the role of pharmacometrics in the drug approval process through its approach to review of applications and by publishing its "guidances." The FDA has gained expertise in pharmacometrics from self-training within and by recruitment of new highly skilled personnel. The value of pharmacometrics continues to be evaluated at the FDA.

1.6 SUMMARY

Pharmacometrics is playing a major role in improving drug development and therapeutics. Improvements in drug development must come through creating and using novel pathways to approval and application of sound scientific principles, partly by applying mechanistic PM models. It is difficult to imagine a more efficient, powerful, and informative drug development process without the expansion of the role of pharmacometrics.

Pharmacotherapy is also in great need of improved dosing strategy selection for the avoidance of adverse events and the improvement in efficacy. This will come through the development of pragmatic PM models that provide knowledge

about drug behavior and how the drug can be optimally used. As more pragmatic PM models are developed, optimal dosing strategies can be implemented. The acceptance of pharmacometrics in drug use and development cannot, therefore, be overemphasized.

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