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PHARMACOKINETIC/PHARMACODYNAMIC MODELING IN DRUG DEVELOPMENT

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■ **Abstract** We propose a framework for considering the role of pharmacokinetic/pharmacodynamic modeling in drug development and an appraisal of its current and potential impact on that activity. After some introduction, definitions, and background information on drug development, we discuss subject-matter models that underlie pharmacokinetic/pharmacodynamic modeling and show how they determine appropriate statistical models. We discuss the broad role modeling can play in drug development, enhancing primarily the ''learning'' steps, i.e. acquiring the information needed for the label and for planning efficient confirmatory clinical trials. Examples of past applications of modeling to drug development are presented in tabular form, followed by a discussion of some practical issues in application. Modeling will not reach its potential utility until it is manifest as a visible and separate work unit within a drug development program. We suggest that that work unit is the ''in numero'' study: a protocol-driven exercise designed to extract additional information, and/or answer a specific drug-development question, through an integrated model-based (meta-) analysis of existent raw data, often pooled across separate (clinical) studies.

INTRODUCTION

In this paper, we propose a framework for considering the role of pharmacokinetic/pharmacodynamic (PK/PD) modeling in drug development and an appraisal of its current and potential impact on that activity. We take a broad view herein of the dose-exposure-effect relationship, one in which (*a*) ''exposure'' can be the concentration vs time profile, or a summary measure such as area under the concentration curve or C_{max} (maximum concentration), and (*b*) ''effect'' may be a pharmacological marker, an index of efficacy, or a measure of safety.

In an effort to reconcile the sometimes conflicting views of ''models'' held by clinical pharmacologists and clinical trial statisticians, we are at some pains to elucidate the separate but interdependent roles of the models of each discipline:

subject-matter–specific PK/PD models for the former, and more-general statistical models for the latter.

The paper discusses first theory and then practice. After this introduction and sections on definitions, background information on drug development, and fixing notation, we define first estimation and inference and then the types of subject-matter models that underlie PK/PD modeling. Following that, we show how the subject-matter models determine the statistical models and then conclude the theoretical development by discussing what role modeling might play in drug development. We then present some examples of the application of modeling to drug development and some practical issues in such application. The paper concludes with some speculation on the future of modeling in drug development.

To maintain focus within the space allotment available, we do not attempt an exhaustive literature review. Rather we focus on key ideas and cite supporting literature as appropriate. We also omit the following topics, all of which are relevant to our subject but which are either somewhat peripheral to it or either more specific or more general than appropriate to the level of abstraction we have chosen: detailed discussion of specific PK/PD models [see Holford & Sheiner (1, 2) and Derendorf & Meibohm (3) for review]; design and analysis of traditional dose-response clinical trials [for example, see Senn (4)]; PK/PD in early (preclinical) phases and transition from animal to man (see 5–10); and the application of modeling to pharmacoeconomics or public-policy decisions [for example, see e.g. Blower et al (11)]. Such modeling is expanding, and PK/PD models are part of a hierarchy of models useful for this purpose.

DEFINITIONS

We offer the following possibly idiosyncratic definitions of terms that are used extensively in this paper: drug development, the information-gathering activities that begin when a lead compound is first introduced into man and that end when the accumulated information is summarized and presented to a regulatory agency for a market-access decision; model (data model; model for data), a mathematical form specifying the probability distribution of random variables representing observations [here drug concentration(s) and effect(s)] in a subject-matter domain, and which may be the composition of several submodels (e.g. one for PK, another for PD), including ones for the distribution of unobservable conceptual entities (called latent variables in certain domains), e.g. drug clearance in the population; pharmacokinetics (PK), the relationship between drug inflow (a more-general view than dose) and drug concentration(s) at various body sites, notably the so-called biophase(s), or site(s), of drug action, and for which subprocesses (submodels) for drug absorption, distribution, metabolism, and elimination determine the relationship; pharmacodynamics (PD), the relationship between drug concentrations and pharmacological effects (sometimes called surrogate effects, but more properly called bioresponses), and the relationship, in turn, of these responses to

clinical outcomes; parameter, a fixed constant serving to quantify some aspect of a model; mechanistic model, a model whose parameters correspond to physical or conceptual entities in the subject-matter domain of the model, e.g. a model of drug distribution to an organ that is parameterized in organ blood flow, volume, and drug diffusivity; empirical model, a nonmechanistic model (a semimechanistic model is the composition of two or more submodels, at least one of which is mechanistic and one empirical); descriptive model, a model that is a priori applicable only to a restricted set of circumstances (designs, patient groups) because values of some or all important design or baseline variables that affect outcomes do not appear explicitly; and predictive model, a model that explicitly incorporates variables quantifying important design and baseline features so that the model can predict outcomes conditional upon arbitrary (and perhaps untested) values of those variables.

DRUG DEVELOPMENT

As discussed previously (12), drug development is an information-gathering process that can be thought of as two successive learn-confirm cycles. The first cycle (traditional phase 1 and phase 2a) addresses the question of whether benefit over existing therapies (in terms of efficacy/safety) can reasonably be expected. It involves learning (phase 1) what is the largest short-term dose that can be administered to humans without causing harm, and then testing (phase 2a) whether that dose induces some measurable short-term benefit in patients for whom the drug is intended to be therapeutic. An affirmative answer at this first stage provides the justification for a more-elaborate second cycle. This next cycle (traditional phase 2b and phase 3) attempts to learn (phase 2b) what is a good (if not optimal) drug regimen to achieve useful clinical value (acceptable benefit/risk) and ends with several [or, for the future, perhaps just one (13)] formal clinical (phase 3) trials of that regimen versus a comparator. If the trial(s) reject the null hypothesis of no incremental benefit of the new drug over the comparator (or occasionally no less benefit), the drug is approvable. Although models are used to assign probability values in the confirmatory analysis of clinical trials, the most credible of such analyses rely on a special class of statistical models, those that make essentially no untestable assumptions. This is a desirable feature, as the fewer the untested assumptions on which a conclusion rests, the less vulnerable to criticism is the conclusion. The independence from assumptions is achieved by focusing inference on the value of a simple statistic whose distribution (the model) depends on controllable study design and not on the origin of the data (i.e. not on a model for the data). An example is when the number of beneficial outcomes in a group randomly assigned to new drug treatment is compared with the number of such in a group randomly assigned to control treatment. The probability that the observed difference in frequencies would arise by chance under the null hypothesis can be assessed using Fisher's exact test, which depends for its validity only

on the validity of the randomization and not on the biology underlying the outcomes.

Occasionally, the connection between observed outcomes and conclusions is less direct than in the above example, and inference requires a more-sophisticated model, a data model. For example, when the difference in mean outcomes between drug and control groups is to be compared using a *t* test, the validity of the inference depends not only on the validity of the randomization, but also on the validity of the assumption that the distribution of outcomes in each group is described by a normal probability law, with identical variances. (In fact, this dependence is weak: The test performs well even when this assumption is not strictly true.) Even in such cases, however, the model is of a particularly simple type: It is a descriptive model of the distribution of the data (or a statistic) under the null hypothesis.

In contrast to the confirming phases of drug development, the learning phases entail so-called explanatory analyses, i.e. analyses that estimate the quantitative relationship between inputs and outcomes according to some mechanistic view of the relationship (see below). What we call inputs are such things as drug dose and timing, patient characteristics, disease stage, etc, and the outcomes are observable clinical results, such as the time between starting treatment and the first occurrence of an untoward event (such as recurrence of neoplasm). Although one might try to view learning as an exercise in confirming (for example, one might test the null hypothesis of no difference between outcomes of small versus large doses), it is far more natural to view learning as the task of constructing a model of the input-outcome relationship itself. This relationship is usually expected to be far more complex than the null hypothesis, which states, with respect to drug inflow at least, that outcome is unrelated to it. A crucial distinction is not only what is being modeled (the drug action, or alternative hypothesis versus the null), but also that the model sought is a predictive one, not a descriptive one. A goal of phase 2b is to predict the best dose for each patient type—old, young, fat, thin, etc—which is a broader objective than to assess the relative value of only those particular doses that happened to be used in the phase 2 trials. Thus, a model suited to learning must interpolate between, and extrapolate beyond, the value of the conditions of the actual study or studies available. The need for a predictive model directly drives the types of models that can be considered as useful learning model candidates—most important, they must be mechanistic as opposed to empirical. That is, they must (*a*) extrapolate beyond the bounds of the design on which they are defined (models must explicitly express the values of those bounds), and (*b*) provide credible extrapolations (models must incorporate the current scientific understanding of their subject matter field).

Empirical models do neither. A mechanistic model, in turn, must be causal: It may not predict outcomes at a given time conditional on events that have not yet occurred. These requirements, as shown below, determine the types of statistical models that are candidates for learning models.

Much has been written about inference for hypothesis testing. There is no need for a review article in a pharmacology journal on this essentially statistical topic. Rather, this article focuses on the uses of scientific predictive models in drug development and on their application primarily to learning, although we also consider their (more controversial) use for confirmation. A companion article (13a) goes into greater detail on a particular new use of predictive models, the activity of designing confirmatory (and learning) trials using computer simulation of predictive models of those trials.

NOTATION

Before proceeding further, it is useful to introduce some notation so that the ideas presented above, and to be elaborated on further below, can be stated with sufficient precision. We consider the unit information-gathering activity in drug development to be the clinical trial and therefore offer notation for this context. In a clinical trial, individuals are chosen for study, are observed for baseline covariates such as sex and age, denoted **X** (boldface indicates vectors and matrices), are assigned to treatments, and are treated and observed for outcomes **Y,** according to a plan, or nominal design, denoted **D.** Nominal design includes all ostensibly controllable factors affecting the conduct of the trial, e.g. the types and number of subjects, the treatments to be administered, the outcome measurements to be made (and the schedule of those measurements), and the type of data analyses to be performed. It thus defines all the procedures to be followed, all the data to be gathered, and, not to be neglected, the manner in which conclusions (inferences) are to be drawn from those data, including how to deal with missing data (see below). Nominal design depends, therefore, on **X,** which may be indicated by the notation $\mathbf{D^n} = \mathbf{D^n}|\mathbf{X}$.

Nominal design is an abstract ideal. In fact, in any real study, deviations from nominal design are inevitable (e.g. some patients will not follow treatment instructions faithfully). The actual design, i.e. the realized value of the controllable variables, number of individuals, treatments, etc, is denoted **D.** Technically, one distinguishes between the random variable, say **X,** i.e. the potential baseline covariate values of an individual, and **x,** the particular realized value of **X** for a given individual. In an abuse of notation, we use the symbol **X** (and similarly **D, Y**) to refer to both of these quantities and hope that the context will make clear which is meant.

The symbol [**A**] denotes, generically, the probability distribution function for **A,** if it is a continuous random variable, or probability mass function, if it is discrete. For two (or more) random variables **A** and **B,** the symbol [**A,B**] denotes their joint probability distribution, [**A**] denotes the marginal distribution of **A** ($\int$[**A,B**]d**B**), and [**A**|**B**] denotes the conditional distribution of **A** given the value of variable **B** ([**A,B**]/[**B**]). Implicit in this paper is that the models we discuss are parametric models, i.e. they have definite mathematical forms, quantified by a

finite (small) number of fixed parameters. We denote the parameters of a distribution generically as **θ,** and where we wish to draw attention to these, we write, for example, [**A; θ**].

ESTIMATION AND INFERENCE FOR PROBABILITY MODELS

Estimation and inference for full probability models is almost always based either on likelihood or on Bayes theory [for a general discussion of these methods as applied to the types of models usually encountered in PK/PD, see Davidian & Giltinan (14); for additional emphasis on Bayesian methods, see Gelman et al (15)]. These two modes of inference are similar; indeed, under the latter view, the former is simply a special case.

With the likelihood approach, a point estimate of the parameter of a model is the parameter value that maximizes the data probability under that model (the estimate is called the maximum likelihood estimate). This amounts to choosing to believe that the true state of nature is, given the chosen form of the model, the instance of that form under which the data that were actually seen are most probable. Likelihood theory also provides a means of assessing the degree to which other states of nature (parameter values) are compatible with the data and, hence, provides a plausible interval or set of parameter values, as those values not contradicted by the data at a certain fixed level of probability.

Bayes theory goes a step further by providing a coherent method of modifying a current view of the state of nature in light of newly acquired data. It does so by regarding the model parameter as an unknown random quantity with a prior distribution that expresses one's current belief as to its likely value (distribution). Bayes theorem is then used to combine this prior distribution with the data likelihood to yield a posterior distribution that represents an updated view of the parameter value, incorporating both prior knowledge and new evidence. The updating procedure involves integration, rather than maximization, a numerically more-challenging problem. The posterior distribution expresses the probability of every possible parameter value; a plausibility region, such as that provided by the likelihood procedure, should it be desired, is then an immediate consequence.

For the purposes of this paper, it makes little difference which of these two methods is contemplated. The central point is that they share the requirement for a probability model for the data. Both are to be distinguished from frequentist theory, which provides no general procedure for estimating complex data models, although certain ad hoc frequentist methods of inference have well-established desirable properties for certain such models.

The past several decades have witnessed major advances in our ability to actually provide maximum likelihood or Bayes estimates of complex models for data. At this point, feasible procedures exist to provide either type of estimate for

at least moderately complex models with moderate-to-large (but not very large) data sets (for example, see 14).

MODELS

Once a nominal design is chosen, a clinical trial can be thought of as a series of three steps, each generated by a different model (or submodel). First, a study population is drawn from the model [**X**]. Given a population and a nominal design, the study can be executed. An actual design (**D**) arises from the model [**D**|$\mathbf{D^n}$,**X**] and ultimately results in outcomes, according to the model [**Y**|**D,X**]. (Note the assumption that given the actual design **D,** the nominal design $\mathbf{D^n}$ does not influence the outcomes.)

The above is not quite correct. Strictly speaking, [**D**|$\mathbf{D^n}$,**X**] should be written [**D**|$\mathbf{D^n}$,**X,Y**], where (in an abuse of notation) causality demands that the dependence on **Y** of any elements of **D** associated with time t be limited to those elements of **Y** associated with times $s < t$. Likewise, [**Y**|**D,X**] is written [**Y**|**D,X,Y**], where again the dependence of elements of **Y** on elements of **D** or other elements of **Y** is understood to obey the requirements of causality. We now discuss in some further detail the three models defined above.

Covariate Model: [X]

A great deal of data has been accumulated on baseline covariate values in populations as part of clinical trials and also by health care organizations. One may hope to use these empirical distributions for [**X**] and thereby avoid formal modeling. Models [**X**] are important for simulating clinical trials (see below) (see also 13a). They are less important for other uses of modeling in drug development, as the particular pattern of covariates of the subjects in a given study can be regarded as fixed and the analysis conditioned on them.

Predictive models of drug action (see below) will usually depend on covariates, and it may be of interest to discover this dependence, for example to determine optimal dosing for a population subgroup such as the elderly. However, the frequency of the elderly in the population (i.e. [**X**]) is not of central importance; what matters is the relationship between outcomes and being elderly (i.e. [**Y**|**X**]).

Deviation from Protocol Model: [D|D^n,X,Y]

Following the conceptualization of Urquhart (16), deviations from protocol can be divided into three types: (*a*) initiation deviations, e.g. certain types of individuals may selectively refuse to enter the study; (*b*) compliance (execution) deviations, e.g. some individuals who enter the study may not comply fully with instructions, (missing doses, clinic visits, etc); and (*c*) termination deviations, i.e. individuals may drop out of the study prematurely for many possible reasons.

Scientific models are unlikely here, as deviations may often depend on such nondeterministic things as personal preference, forgetting, and the like. As for [**X**], one may hope to use empirical probability distributions based on accumulated experience with deviations from protocol in past clinical trials. Parametric models for compliance deviations have also been discussed in the literature (e.g. 17, 18). For reasons discussed more fully below, the model [**D**], unlike the model [**X**], is important not only for simulation, but also for clinical trial interpretation.

Outcome Model: [Y|X,D,Y]

The predictive models of greatest immediate relevance to drug development, and those of greatest relevance to this article, are input-outcome models that relate drug inflow (part of **D**) to clinically important outcomes (part of **Y**), conditional on other inputs, **X.** These models are often referred to as pharmacokinetic/pharmacodynamic (PK/PD) models, as they tend to incorporate submodels for these processes.

Causality is assumed to flow from drug doses through PK processes to concentrations, and thence to pharmacological effects and ultimately to clinical outcomes. This notion involves the intuitively obvious but powerful assumption of conditional independence: Any entity on this causal path is completely determined, given full knowledge of the immediately preceding entity. Thus, given full knowledge of drug concentrations, knowledge of drug inflow contributes nothing to knowledge of pharmacological effects.

This causal view allows one to consider exposure as the conditioning variable for a PD analysis, i.e. when **Y** is restricted to PD observations, one may use the model [**Y**|**X,***E*,**Y**], where *E* is exposure. *E* may denote any of the entities on the causal path from drug to pharmacological effect: drug inflow rate, plasma drug concentration versus time, biophase drug concentration versus time, the hypothetical level of some signaling or bioeffector substance versus time, or some integrated measure of systemic exposure such as area under the concentration curve (see 19).

Which exposure variable to use is determined by where the rate-limiting step between drug input and PD effect lies. If all processes preceding the PD process are rapid relative to it, a simple nonlinear transformation of drug inflow versus time will serve as well as any more-elaborate exposure measure to drive the PD model. In contrast, if drug distribution to the biophase is rate limiting, then a model for this dynamic process will be indicated. In essence, the concept of exposure allows the explicit appearance of time in the model [**Y**|**X,***E*,**Y**] to be eliminated, relegating it to the model [*E*|**X,D**] (or perhaps the more elaborate [*E*|**X,D,Y**]).

The deviation from protocol model and the outcome model have thus far been presented as models for generic individuals. But these two models must, like the model for **X,** deal with the variability from individual to individual and within an individual over time. This is discussed below.

STATISTICAL ISSUES IN MODELING

Although it is not always the case, modeling the distribution of a random variable can generally be regarded as two distinct tasks: modeling its mean or expected value (or some other natural ''location'' parameter), and modeling its variability around that mean (variance, or some other natural ''scale'' parameter). The model for the expected value generally captures most, if not all, of the mechanistic subject-matter science and is usually the province of the subject-matter expert. In contrast, statisticians are generally most familiar with and expert in modeling random variability. To some extent this separation is unfortunate, as the modeling choices made for each subtask are interdependent. We take the opportunity here to remark on the interaction between them, primarily to point out how the need for mechanistic models limits the options for statistical modeling. Because subtle statistical issues do not arise for [**X**], for concreteness and clarity of presentation, we limit our discussion in this section to a particular submodel of the outcome model, the PK submodel, but the points made apply equally well to the other parts of the outcome model and to the deviation from protocol model.

Exchangeability and Conditional Independence

The idea of exchangeability is a statistical concept, important to modeling in general and to the issue of predictive versus descriptive models in particular. Data are exchangeable if the joint probability model for all of them is unchanged under a permutation of data indices, i.e. exchanging the position of one datum for that of another. It is usually appropriate to model exchangeable data as independent and identically distributed. Thus, if one can make data exchangeable by appropriate use of covariates and/or subject-specific parameters (see below), the modeling task is made much easier, as one need model only a generic instance of the data (as indeed we have been doing thus far). The joint distribution then becomes simply the product of instances of the generic distribution. In particular, it will almost always be reasonable, introducing the subscript i to distinguish among individuals, to assume that given **X** and population parameters **θ,** observations from different individuals are independent, i.e.

$$[\mathbf{Y}_1, \mathbf{Y}_2, \ldots, \mathbf{Y}_i, \ldots \mid \mathbf{X}_1, \mathbf{X}_2, \ldots, \mathbf{X}_i, \ldots] = [\mathbf{Y}_1|\mathbf{X}_1]\,[\mathbf{Y}_2|\mathbf{X}_2]\,\ldots\,[\mathbf{Y}_i|\mathbf{X}_i]\ldots. \quad 1.$$

Explicit reference to covariates is crucial to establishing exchangeability. Consider, for example, two observed drug concentrations, Y_j and Y_k, drawn from the same individual. A possible model for the distribution of either one might be $[Y] = N(\mu,\sigma^2)$, a normal distribution with mean μ and variance σ^2. For Y_j and Y_k to be exchangeable and independent, then at least the following two assertions must

hold. Both concentrations are (*a*) drawn after a dose of the same magnitude and (*b*) drawn at the same time after the dose.

If both assertions hold, then the model is an adequate descriptive model of either observation, and the joint distribution of the two observations is $N(\mu,\sigma^2) \times N(\mu,\sigma^2)$. However, if the assertions do not hold, then the observations are not exchangeable and may not be independent, i.e. the above model cannot be used. In contrast, if the model $[Y] = N\{(D_s/V)\exp[-(Cl/V)t_s], \sigma^2\}$ were used instead, where $\mathbf{X}_s = (D_s,t_s)$ and $\boldsymbol{\theta} = (V,Cl)$ for $s = j,k$, then the data would become exchangeable, and independent conditional on $\mathbf{X}$ and $\boldsymbol{\theta}$, and the joint density of Y_j and Y_k would be the product of two instances of the model. This latter model qualifies as a predictive model, as it allows prediction (at least within the individual to whom it applies) of concentrations at other times than (t_j, t_k) after doses other than (D_j, D_k), i.e. predictions of outcomes of experiments not yet performed.

Marginal Models Versus Conditional Models

Although exchangeability simplifies things enormously, as one need consider only a model for $\mathbf{Y}_i$ to have a model for $(\mathbf{Y}_1,\mathbf{Y}_2, \ldots)$, $\mathbf{Y}_i$ itself—considered as a set of observations from an individual on a given occasion—is still multivariate, and its elements are not independent, as they all arise from a common design that is administered to a single ''system,'' the subject *i*. A so-called marginal model attempts to deal with this intraclass correlation by positing an empirical model for the correlation between the elements of $\mathbf{Y}_i$. Thus, if each individual had five PK measurements, a saturated empirical marginal model would posit a 5×5 covariance matrix for each $\mathbf{Y}_i$, which might be regarded as constant across individuals, thereby introducing $5 \times 6/2 = 15$ so-called nuisance parameters into $\boldsymbol{\theta}$, in addition to the more-interesting population parameters, such as population average (marginal) drug clearance (CL) and volume (*V*).

The great advantage of this approach is that it allows the modeler to focus on the issues of concern (population average physiology) and allows simple empirical models to handle the statistical complication of intraindividual correlation, which may be of little intrinsic scientific interest. Unfortunately, the price of this convenience can be high. First, how can one be certain that intraindividual variability is not of scientific interest? Avoiding explicit modeling of certain data features runs the risk of hiding important insights. More important, however, this approach provides only a descriptive, not a predictive, model, thus restricting its applicability. In particular, in this example, each person must have five (or fewer) PK observations. Second, for these observations to share a common correlation matrix, they must at least all be taken according to the same time schedule after the same dosage regimen. The approach will fail if each individual receives a different regimen (as is inevitable if medications are self-administered) and/or is observed according to different schedules (inevitable for outpatient studies).

Because of this failing, an alternative, so-called hierarchical model approach has gained currency among PK/PD modelers. This approach establishes within-

individual exchangeability, independence, and predictiveness, by conditioning on individual-specific **X** and **D** and individual-specific parameters. Thus, a minimal hierarchical model for $\mathbf{Y}_i$ is

$$[\mathbf{Y}_i|\mathbf{X}_i, \mathbf{D}_i; \boldsymbol{\theta}] = \int [\mathbf{Y}_i, \phi_i|\mathbf{X}_i, \mathbf{D}_i; \boldsymbol{\theta}]\, d\phi_i = \int [\mathbf{Y}_i|\mathbf{D}_i; \phi_i]\, [\phi_i|\mathbf{X}_i; \boldsymbol{\theta}]\, d\phi_i, \quad 2.$$

where ϕ_i is the set of PK parameters of individual *i*'s PK model (for example, volume of distribution and clearance), and $\boldsymbol{\theta}$ consists not only of the population mean values of ϕ_i, but also of parameters quantifying the extent of their interindividual variability and of others quantifying the magnitude of errors in measurement of the PK observations in $\mathbf{Y}_i$. The model is called hierarchical because at a first level, the distribution of individual elements of **Y** depends on parameters ϕ_i and design **D** (e.g. dose, time), whereas at a second level of the hierarchy, the distribution of ϕ_i depends on population parameters $\boldsymbol{\theta}$ and baseline covariates **X.** A Bayesian approach adds a third level to the hierarchy: a prior distribution on $\boldsymbol{\theta}$, entailing its own hyperparameters.

Note that under the hierarchical formulation (Equation 2), the only PK model that is required (it appears as an expression for the expected value of the conditional model of the first level) is the one that is most familiar to PK modelers: a PK model for the disposition of a drug in a single individual. This is not simply a fortunate accident, it is a direct consequence of the suitability (and hence the reason this form is chosen) of the hierarchical model formulation for the scientific mechanistic view: Physiology (and pharmacology) operates at the level of individuals, not populations; scientific models are available for the former, not the latter.

Informative Missingness

Of particular concern for data analysis is the possibility that **D** differs from $\mathbf{D}^{\mathbf{n}}$ in a way that depends on the parameters of the model for **Y** (in contrast to the observed **Y;** dependence on the latter is not a problem) (see below). Such so-called informative deviations may occur, for example, if those dropping out of a study of new drug versus placebo do so because they are not improving. If analysis is made conditional on **D,** without taking into account its informativeness, the result is not simply that useful information is lost, but also that bias may result: Even if drug is far more effective than placebo, comparison of outcomes only in protocol completers may well show no group difference, as the only individuals remaining to the end in either treatment group are those who improve. This issue has received much attention in the recent statistical literature (for example, see 20, 21).

In the above example, let *T* denote the time at which an individual drops out and after which no further data are gathered (*T* can be set to infinity for study completers). Let **Y** denote the outcome variable of primary interest, the severity

of illness at fixed times after study treatment begins. The data from an individual is (**Y,***T*), where **Y** consists only of observations scheduled before time *T.*

The standard approach to a dropout problem such as this is somehow to impute the missing data (''last observation carried forward'' is one such imputation scheme) and analyze the now ''complete'' data using the analysis procedure proposed by the nominal design. This approach has many problems, but it may sometimes suffice for a (conservative) confirmatory analysis (but see 21). It is clearly inappropriate, however, to invent data and treat it as real when the goal is a predictive model.

A possibly better approach to dealing with the informativeness of *T* is to subdivide the patients into those with like values of *T* and to perform separate comparative analyses in each group (20). This is tantamount to factoring [**Y,***T*] as [**Y**|*T*][*T*], a so-called pattern mixture model (22), and estimating the first and more-interesting factor only.

The problem with the pattern mixture model approach is that it is neither mechanistic nor predictive. It is not mechanistic because it defies causality: *T* depends on **Y** at *T* (or before), not the other way around. It cannot be predictive because we cannot know an individual's *T* beforehand, and thus cannot know which of the several [**Y**|*T*] models to apply to his data. Note, however, that the model may serve well as a descriptive one for a confirmatory analysis, e.g. of whether benefit is greater in the drug-treated group than in the placebo group at any given level of duration of study participation.

A mechanistic approach factors [**Y,***T*] as [*T*|**Y**][**Y**], a so-called selection model. This model is causal, and the second factor is the model of true interest: the nondropout treatment-response model. The problem with this approach is that one may be forced to make assumptions about the form of [**Y**] that are not testable on the data at hand because key observations are missing, i.e. [**Y**] may not be fully identifiable on the current data. Assumptions based on the subject-matter science (i.e. prior knowledge) and use of a fully Bayesian framework may allow credible inference nonetheless. The use of a selection model formulation becomes both easier and more credible when the additional assumption can be made that [*T*|**Y**] depends not on ''true'' **Y** but only on the actually observed values of **Y.** In this case, *T* is said to be ignorable, as it contains no information about [**Y**] not already available in the observed **Y** itself. If this assumption can be made, one may fit [**Y**] to **Y** and not bother with [*T*|**Y**] if it is not of interest [for recent examples of analyses of the same type of study, an analgesic trial, using selection models with and without the ignorability assumption, see Sheiner et al (23) and Pulkstenis et al (24)].

USES OF MODELING IN DRUG DEVELOPMENT

From the producer's or sponsor's point of view, the goal of (commercial) drug development is market-access approval so profits can be made. From the consumer's point of view, the goal is useful remedies. The producer's profit incentive

is constrained to serve the consumer's needs by regulation, which tries to insure that market access is granted only to products that are likely to produce net benefit when used in the approved manner for the approved class of individuals. For regulation to work as intended, the final regulatory hurdle prior to market entry must be relatively objective. Confirmatory trials and analyses fulfill this criterion, as discussed above, whereas explanatory ones do not. Thus, in theory, modeling can only prove useful to those activities in drug development where great objectivity is not essential (Table 1).

Development decisions—i.e. which molecules will be carried forward, what studies will be done in what order, the design of specific studies on which go/no-go decisions will be based, etc—influence essentially only the producer's risk. Here the consumer's and producer's motivations coincide, and regulation need not be invoked, except to protect the safety of human subjects. Modeling can be useful here by providing credible simulations of studies and development plans (see 13a) that allow their relative merits to be quantified.

The labeling items noted in Table 1 all provide details on the conditions of use required to extract net benefit. If the physician can be assured of adequate safety of an initial regimen, he or she can usually titrate an individual to a useful dosage schedule, making suggested dosage and individualized adjustments merely guidelines, rather than essential. Likewise, cautioning use of a drug in a subpopulation is prudent and does not enhance consumer risk.

The usual intention-to-treat analysis of a confirmatory trial provides estimates of the outcome difference attributable to the prescription of the drug, not of the actual taking of it (25). Yet some indication of the actual benefit to be gained

TABLE 1 Modeling in drug development: activities for which great objectivity is not required

Development decisions
Development Planning
Study design
Labeling
Dosage regimens
Dosage adjustments for special populations
Safety restrictions
Quantifying benefit
Market-access testing
Great potential benefit
High prior presumption of positive benefit/risk
Excessive ''cost'' of objective evidence
More powerful statistical tests

when a drug is taken as instructed is useful and, using current confirmatory trial designs, can be obtained only through model-based explanatory analyses. Such information, even if somewhat uncertain, can only benefit consumers.

Given the discussions above, it is surprising there are any circumstances under which modeling is admissible in testing for the market access decision. Yet where there is great potential benefit, lesser objectivity may be allowed for market access, with appropriate follow-up requirements. This is the basis of the accelerated approval policy of 1992 by the Food and Drug Administration (FDA) (26), used so effectively to allow anti-HIV treatments to be marketed only shortly after preliminary indications of efficacy and safety were available. One may take the recent FDA mandate (13) to consider a single study plus ''confirmatory evidence'' (an unfortunate choice of words, as their ''confirmatory'' is synonymous with our ''explanatory'') as adequate for approval as another step toward blending strictly objective evidence with evidence more sensitive to assumptions, even where great potential benefit is not an issue.

Where benefit/risk appears well known from prior data, market access may be granted based on less-objective evidence. This is the basis for granting ANDA (Abbreviated New Drug Application) approval to generic preparations based on bioequivalence measures. High prior presumption of favorable benefit/risk, combined with the fear that obtaining objective data will either be excessively costly or present unacceptable ethical risks, presumably underlies the recent proposal to grant approval for drugs approved for adults to be used in the pediatric population, based largely on the use of PK/PD modeling to bridge adult and pediatric data (27).

A final, more-technical application of modeling to market-access decisions is its use to assure that confirmatory analyses invoking complex but more-powerful statistical tests do not increase consumer risk. A nice approach is provided by Rubin and coworkers (28, 29). These authors show how the analysis of a clinical trial marred by noncompliance, but fulfilling certain assumptions (such as that access to the experimental treatment is impossible for those not assigned to it), can test the null hypothesis of no drug effect against the (powerful) alternative that a drug acts beneficially among those assigned to it only in those who actually receive it. This alternative contrasts with the usual (less powerful) intention-to-treat alternative, that benefit accrues from assignment, regardless of receipt. In this example, simulation, and hence a model, essentially for noncompliance is needed to assign a *P* value to the more-powerful ''instrumental variables analysis'' statistic. All assumptions are explicit, so that regulators can decide whether they are credible.

EXAMPLES OF MODELING IN DRUG DEVELOPMENT

Table 2, organized to reflect the categories of Table 1 but expanding on it somewhat, cites conditions for the use of modeling in drug development and provides public-domain examples. Table 2 also specifies which types of models and what

sources of experimental data are required for the particular use. The types of experimental data are categorized and denoted as follows: S1, preclinical, in vitro, or in vivo animal; S2, normal human subjects; and S3, diseased human subjects. Note in particular that most of the analyses in Table 2 at least allow, if they do not positively benefit from, pooling of data from multiple sources and studies. The explicit recognition of variation in **X** and **D** by mechanistic models allows such synthesis, which is difficult if not impossible with the empirical models used for confirmatory analyses. This represents perhaps the greatest single virtue of the model-based approach.

The examples listed and discussed in Table 2, and those discussed above, confirm that mathematical modeling has achieved a degree of maturity that allows it to make a useful contribution to drug development. This point has also been made from various perspectives in several recent survey papers (for example, see 30–35).

PRACTICAL ISSUES FOR MODELING

Despite the overwhelming evidence of utility, as provided above, modeling is not yet in the mainstream of drug development. This is partly because, despite repeated claims that PK and PD principles should guide drug development (5, 30, 74–76), the potential of the approach is still underestimated. Among the prominent factors preventing full application of PK/PD modeling, Reigner et al (32) cite the variable understanding of PK/PD concepts among the members of the (project) teams in charge of development within pharmaceutical companies. Notwithstanding, the key problem, in our opinion, is that the potential rewards of PK/PD modeling (as defined in this paper) cannot be realized without a substantial investment of time and resources, and any additional investment of time in development is perceived nowadays as a delay.

Indeed, modeling will delay development if it is not adequately planned for and integrated into the clinical development program. Until modeling gains the same recognition, sponsorship, and stature as other drug developmental activities, such as in vitro or animal in vivo studies, it cannot deliver on its promise to increase efficiency and comprehensiveness of knowledge. How this might be accomplished is discussed further in the next section.

In contrast, we do not believe that regulatory attitudes toward modeling are important factors impeding its greater application. Indeed, regulatory attitudes toward using model-based analyses as part of a submission for approval for market access seem generally in line with the theoretical positions presented herein (see above). Use of explanatory analyses for labeling have been encouraged for years [e.g. use of the so-called pharmacokinetic screen (54, 77)]. Several ICH (International Conference on Harmonization) guidelines [e.g. ICH4 on dose-response information (78)] make explicit reference to modeling for such purposes as dose ranging, and the US FDA has issued a *Guidance for Industry* on popu-

TABLE 2 Pharmacokinetic/pharmacodynamic (PK/PD) modeling in drug development: examples and features[a]

Area	Goal	Data source	Pool data[b]	Add'l models[c]	Examples (References)
General	Improve methodology for drug-effect assessment, evaluate value of pharmacological surrogates	S1—S3	+	−	One major task of (and opportunity for) clinical pharmacology is to help identify and validate PD surrogates (36). As recent examples in the cardiovascular (37) and CNS (38, 39) areas illustrate, mechanistic PK/PD understanding (and appropriate modeling procedures) will be needed in order to ascertain the degree of validity of surrogates for efficacy determination.
	Use observational data	S2, S3	+ +	**[D|X]**	A Markov mixed effect model was proposed to describe and quantify observational compliance data (collected via electronic medication monitor systems) in HIV-positive patients taking zidovudine (18, 40). The model is likely to have broad validity in other therapeutic areas, and to serve as a useful tool for simulation and model-based analysis of clinical trial data. The use of observational data on drug systemic exposure from a clinical trial with primary therapeutic objectives provides additional insight into the dose-effect relationship (30), as it also does in complex situations such as anti-HIV combination therapy (41).
Preclinical	Explore implications of data/models	S2, S3	+ + +	**[X], [D|D^n,X]**	Based on a model of infectious and noninfectious HIV virions, model-based analysis of existing data showed that direct measurement of infectious viral load provided sufficient information to estimate antiretroviral drug efficacy (42).

	Screen lead compounds	S1	−	−	Physiologically based PK/PD modeling helped select the short-acting intravenous sedatives that were most likely to improve on midazolam (32).
	Develop PK/PD models	S1	+ +	−	A variety of effect measurements and mathematical modeling techniques were developed using animal experiments with psychotropics (7), opioids (9), anti-convulsants (10), and cardiovascular agents (8).
	Animal-man scale-up	S1	+ + +	−	Evidence that reliable predictions of clearance, PK parameters and Conc × time & Effect × time profiles in man can be made from animal data is accumulating (32, 43). (For a review, see 6.)
Drug development (plan)	Guide dose-escalation in entry into human studies	S1	−	−	Successful PK/PD-based choices of dose range and regimen have been reported in such diverse therapeutic areas as oncology, anticoagulant therapy, and infectious disease (32).
	Select lead compound	S1	−	−	Mechanistic mathematical modeling offers a way to determine the relative potencies of compounds with similar modes of action, e.g. 5alpha-reductase inhibitors (44) and benzodiazepines (45).
	Discontinue indication	S3	+	−	Model-based predictions were corroborated by clinical trial results, and provided a rationale for stopping development of a new formulation of interferon with improved PK. PK/PD modeling revealed that increasing the circulating half-life of interferon 2a twofold was of limited therapeutic benefit (32, 46).

(continued)

TABLE 2 *Continued*

Area	Goal	Data source	Pool data[b]	Add'l models[c]	Examples (References)
	Which drug/drug interactions require study	S1–S3	+	–	Assessment of drug/drug interactions in vivo may be achieved through ''many'' interaction studies, as for ciprofloxacin (47). Mechanistic model-based PK analyses (48, 49) help assess which interactions are likely and provides novel quantitative tools for study design and analyses.
	Select dosage and/or regimen for phase 2 and/or phase 3	S1, S2	+ +	**[X]**	Several drug companies found that dual modeling of exposure-efficacy and exposure-safety relationships in phases 1 and 2a allows more reliable and sometimes earlier determination of the correct dose for pivotal therapeutic trials (32, 50).
	Design phase 3 trial	S1–S3	+ + +	**[X], [D|D^n,X]**	Model-based study design has been used in transplantation (51), Alzheimer's disease (52), and HIV therapy (42). Clinical trial simulation is currently an area of active research (13a).
	Design trial for special populations	S2, S3	+ + +	**[X], [D|D^n,X]**	Studies in special populations (e.g. the very young or the very old) impose severe restrictions on data collection (e.g. sparse blood sampling for PK) (53, 54), which imply model-based data analysis. This also applies to studies of diseases with high prevalence only in developing countries [e.g. malaria (55)].

	Special objectives	S3	+	**[X]**	Applications of modeling include the evaluation of impact of dosing omissions of a dopaminomimetic on prolactin suppression (56), the description of change in action of levodopa in presence of an inhibitor of its metabolism (57), and the measurement of in vivo parameters (e.g. insulin sensitivity) in provocation tests (e.g. intravenous glucose tolerance test) (58, 59).
Labeling	Dosage regimen	S2, S3	+ + +	**[X]**	The recommended initial dose of ketorolac for postoperative pain was based on the model-based relationship between dose, time postdose, and percentage of patients with adequate pain relief (60).
	Assess new formulation	S2, S3	−	−	Assessing the value of a new formulation through model-based prediction of concentration and/or effect time courses can provide a rationale for, e.g., a long-acting PEG-interferon (61) or against further development [e.g. an early formulation of PEG-interferon (46) or lithium in manic-depressive disorders (62)].
	Assess need for specific population study	S2, S3	+ + +	−	Integrated model-based analysis of existing data (i.e. in numero investigations; see below) can provide a rationale for dosage adjustment in special patient populations, e.g. remifentanil (63), ondansetron (64), S12024 (52). Model-based evidence, if convincing, may obviate the need for specific experimental studies, e.g. in renal insufficiency.
	Safety restriction	S3	+ +	−	A population PK analysis helped to delineate the risk of the anti-cancer agent docetaxel in patients with liver insufficiency (65, 66).

(continued)

TABLE 2 *Continued*

Area	Goal	Data source	Pool data[b]	Add'l models[c]	Examples (References)
	Quantity benefit ''confirmatory''	S3	+ +	**[D|D^n,X]**	Variable compliance affects the mean outcome in the treated group: A model-based ''instrumental variables'' analysis was shown to provide an unbiased estimate of the fully compliant response, with minimal assumptions (29).
	Integrated summary of PK and PD	S2, S3	+ + +	**[X], [D|D^n,X]**	The Dose-AUC relationship of saquinavir was characterized over a broad range of doses, conditions, and formulations, using data from 23 human studies (67). An ambitious development would be the integrated model-based analysis of all pre-ANDA PK (or PD) data for a new drug, as part of the regulatory dossier. We do not know of any such example.
Market-access testing	Bridging (ethnic groups)	S2, S3	+ + +	−	PK/PD modeling has been used to bridge clinical data (and adjust dosage) across races (e.g. Caucasian and Japanese) (68). This provides an opportunity for making global development plans ''leaner'' and less demanding of patient populations.
	Extended or meta-analysis of prior studies for ''confirmatory'' evidence	S2, S3	+ + +	**[D|D^n,X]**	Model-based meta-analysis of pooled PD data from multiple clinical studies with different designs helped strengthen the claim for efficacy and provided quantitative estimates of type and magnitude of action [e.g. for tacrine's action on disease progression in Alzheimer's disease (69, 70) and felodipine in hypertension (71)].

Extension to new population (e.g. pediatrics)	S1–S3	+ + +	−	Mechanistic modeling, e.g. for valproic acid (72) and erythropoietin (73), provided a framework for extrapolating PK and PD from adults to pediatrics, with substantial improvement over empirical allometric scaling.
Model-based tests of efficacy	−	−	**[X], [D|D^n,X]**	The power of a test of the null hypothesis vs the instrumental variables alternative (drug acts only in those who take it) is greater than that of the conventional ITT approach (drug acts in all assigned to it, regardless of whether it is taken or not) (29; see text).

[a]CNS, Central nervous system; PEG, polyethylene glycol; AUC, area under the concentration; ANDA, Abbreviated New Drug Application; ITT, Intention-To-Treat.
[b]+, The degree to which the analyses will profit from pooling data from several studies.
[c]Models needed in addition to input-outcome model, **[Y|D,X]**.

lation pharmacokinetics (79), which opens the door to widespread application of mixed-effects predictive models. The guidance stresses the need for high standards of quality for both data and modeling methodology. A similar initiative was recently taken by the Australian authorities (35). We have already referred to the FDA *Modernization Act* (13) and the recent FDA guidance on pediatrics (27) as evidence that the FDA will accept scientific model–based evidence for efficacy where there is high prior presumption of same, and/or where strong empirical evidence is difficult or impossible to obtain.

PERSPECTIVES

We view future developments in the following areas as crucial to progress.

Good Practices

The paper by Peck et al (13a) largely reflects the consensus of a recent conference (80) (see also http://www.dml.georgetown.edu/depts/pharmacology/cdds/SDDGP.html), where good practices in modeling and simulation of clinical trials are discussed and summarized in a consensus paper. Improved practices for simulation will have major positive impact on other modeling activities in drug development, because the essential requirements for good practice are the same: transparency, clarity, completeness of documentation, and parsimony.

Legitimacy of Modeling

Modeling will not reach its potential utility until it is recognized as a visible and separate work unit within a drug development program. We propose to call that unit an in numero study, i.e. a protocol-driven exercise designed to extract additional information, and/or answer a specific drug-development question, through an integrated model-based (meta-) analysis of existent raw data, often pooled across (clinical) studies. For the in numero study to be recognized as a separate work unit, at least the following changes in the organization of the development process will be required: (*a*) greater continuity of scientific personnel between phase 1 and phase 2; (*b*) increasing involvement of scientists with modeling backgrounds at the beginning of and during clinical development; and (*c*) participation of pharmacometricians (individuals specifically skilled in mathematical modeling and the subject matter of PK/PD) on pivotal team decisions (e.g. through provision of key model-based computer simulations) (see 13a).

Modeling Databases

An impressive variety of PK/PD models have already been defined and applied to numerous drugs. If such modeling is to become even more useful and efficient, a database of accumulated experience (models and results) will be indispensable.

Needless to say, developing, maintaining, and updating such a database is a formidable task; drug-development scientists do not yet have even a common vocabulary (witness our need to define notation in this article).

Increasingly, drugs are being developed that exhibit high-affinity interaction only for specific receptors. Quantitative signals of such specific interaction (''biomarkers'') will undoubtedly be forthcoming and will serve as surrogates for clinical efficacy. Thus, we may expect the future to bring richer and more-detailed PK/PD data, and hence greater opportunity for informative modeling. Yet such modeling faces the following difficulty: Most of the (new) data on drug kinetics and dynamics is generated by the pharmaceutical industry, whereas most of the aggregated (and cleaned) data across compounds within a given class resides in regulatory agencies (e.g. FDA), and much of the talent and time required for developing models is to be found within academia. A cooperative model-building effort is therefore necessary and will be facilitated by the evolution of information technology. Even if technical difficulties are surmounted, however, collaboration implies the sharing in the public domain of new and potentially valuable information, and business practices designed to impede leakage of such information will present barriers to progress.

Methodology

Advances in measurement, modeling, and computation are likely to further expand the spectrum of application of PK/PD modeling in drug development. In the past decades, major progress has been made in developing chemical assays of drugs and metabolites in multiple body fluids, and most notably in developing reliable, sensitive, reproducible, quickly responsive, and noninvasive in vivo measurements of drug effects in man (81–83).

Progress in modeling goes hand-in-hand with progress in measurement. The first steps in the pathway from dose to (clinical) effect (concentration in blood, concentration in biophase, mass-action effect on receptors, and thence on the dynamics of a signaling molecule) are relatively well understood in principle, if not in detail in every case, and prototype-model schemas exist that can be elaborated parametrically or nonparametrically to suit the circumstances (19, 45). However, models in several key generic areas are missing or need considerable improvement.To discuss this only briefly:

1. [$\mathbf{X}$]: Systematic differences may exist between patients recruited to studies and those in the population ultimately to be treated.
2. [$\mathbf{D}|\mathbf{D}^{n},\mathbf{X},\mathbf{Y}$]: Compliance and dropout are receiving increasing attention in the statistics literature (17, 18, 23, 84), as analyses conditioned on these become observational studies, subject to confounding (25). Standard remedies (e.g. intention to treat, last observation carried forward) even in the pure confirmatory context can be shown not always to be conservative (21). Analyses incorporating compliance will have to deal with missing data (not all compli-

ance is observed), and for this a model for compliance is needed. A Markov mixed-effects model (18) is a start but requires further validation and improvement.

3. [**Y**|**D,X,Y**]: Mechanistic physiological models are high dimensional. They can be made practical by limiting the degrees of freedom through informative prior distributions in a full Bayesian analysis (for example, see 85). Models for chronic-disease progress are often simple (e.g. linear with time), especially in cases where the timescale of a clinical trial is short relative to that of the progression of disease. Nonetheless, in any real trial, disease progress is confounded with placebo effect for all patients, and thus sorting out progress/placebo from progress/placebo/drug can be a difficult exercise in identifiability (for an interesting example, see 69, 70). Mechanistic models for circadian variation in PK/PD (for example, see 37, 86) or the link between exposure and adverse effects (for example, see 87) are not yet well developed and require further work.

Essential to increased application of PK/PD modeling techniques has been and may remain the spectacular increase in computational power of the past decade. This has made practical such computationally intensive numerical techniques as (*a*) Markov Chain Monte-Carlo methods for estimation of full (Bayesian) probability models of data (88), (*b*) bootstrap and other sample-reuse methods for honest inference from complex-model analyses (89, 90) [use of this approach has also been suggested in a recent draft by the FDA guidance on bioequivalence for determining confidence bounds (91)], and (*c*) simulation of complex models for experimental design (see 13a).

The view that modeling merits increased application to clinical investigation appears to be shared by others; for example, recent papers appearing in the statistics literature (92, 93) emphasize the value of model-based approaches to clinical biostatistics, the key role that the biostatistician can play as a modeler (in the sense used herein), and, if he is to do so, the fact that he will need increased understanding of the subject-matter science (here, PK/PD).

In our view, the future is bright for increased application of modeling in drug development, as such application is simply a means to, and manifestation of, the transformation of the intellectual basis of drug development from empiricism to science. Such transformations in other domains have inevitably entailed uncomfortable change, but just as inevitably they have brought rapid and spectacular progress.

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