Quantitative Disease, Drug, and Trial Models*

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Key Words

model-based drug development, regulatory decisions, simulation, drug development, exposure response, trial design

Abstract

Quantitative disease-drug-trial models allow learning from prior experience and summarize the knowledge in a ready to apply format. Employing these models to plan future development is proposed as a powerful solution to improve pharmaceutical R&D productivity. The disease and trial models are, to a large extent, independent of the product, but the drug model is not. The goals are to apply the disease and trial models to future development and regulatory decisions, and publicly share them. We propose working definitions of these models, describe the various subcomponents, provide examples, and discuss the challenges and potential solutions for developing such models. Building useful disease-drug-trial models is a challenging task and cannot be achieved by any single organization. It requires a consorted effort by industry, academic, and regulatory scientists. We also describe the strategic goals of the FDA Pharmacometrics group.

INTRODUCTION

Pharmaceutical research and development are reported to be inefficient (1). About 50% of the registration trials (so-called Phase III trials) fail mainly because companies employ one-size-fits-all development strategies. A majority of the trials are reported to fail due to lack of differentiation from placebo (i.e., effectiveness). For example, only 14% of 39 depression trials were successful in terms of effectiveness (2). Other causes of failure include unanticipated safety problems and commercial reasons. Our own experience at the FDA suggests that failure to utilize prior knowledge often accounts for trial failure (3–5). Prior knowledge refers to both drug-specific and non-specific information such as placebo effect and the disease course.

The properties of drug products, with respect to their pharmacokinetics (i.e., exposure) and pharmacodynamics (i.e., response) as measured by effects on biomarkers and clinical outcomes, are routinely characterized during drug development in a variety of species. The information generated across drug development can be systematically compiled to guide future drug development and regulatory decisions. The hypothesis proposed by several groups is that systematic modeling and simulation-based trial design will lead to more successful trials (6–9). These reports also reflect the fairly routine use of exposure-response modeling to make development decisions. A common conclusion is that more careful exploration of drug properties early in development is critical. In addition, to allow more efficient planning during the early phases of drug development there is a need for the accrual of disease and trial knowledge from across development programs (10, 11). We present a conceptual framework for quantifying disease, drug, and trial information that will help guide future development plans. Disease-drug-trial models are recommended in the FDA Critical Path document as a potentially valuable tool to improve the predictability and productivity of the drug development process (12).

QUANTITATIVE DISEASE-DRUG-TRIAL MODELS: WHAT ARE THEY?

Disease-drug-trial models are mathematical representations of the time course of biomarker and clinical outcomes, placebo effects, a drug's pharmacologic effects, and trial execution characteristics for both the desired and undesired responses. **Figure 1** depicts the general concept of quantitative disease-drug-trial models. The disease and trial models are described in detail below.

Disease Model

Disease models quantify the relevant biological (or pathological) system in the absence of drug. The three major submodels of the disease model include (*a*) the relationship between biomarkers

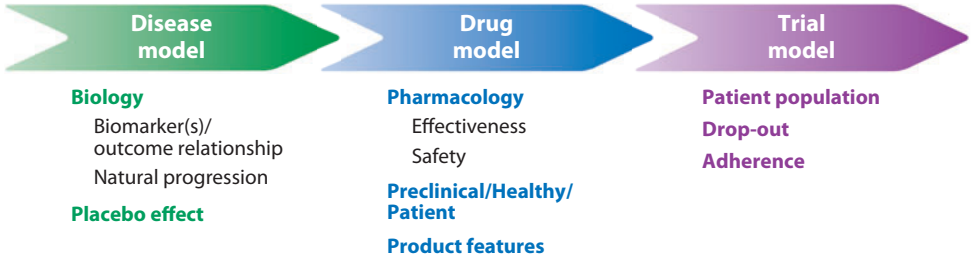

Figure 1

The conceptual depiction of quantitative drug-disease-trial models and their various submodels, including those for product features such as the biopharmaceutical characteristics.

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and clinical outcomes, (*b*) natural disease progression, and (*c*) placebo effect. Although not strictly disease-related, placebo effects are another important piece of disease knowledge. For the sake of simplicity, we have categorized placebo effects as a third component of disease models. Another representation would have been to consider placebo as an additional pharmacologic effect. The degree to which disease mechanisms are understood varies widely. There are three general approaches to developing disease models: systems biology (13), semimechanistic, and empirical models (14). Systems biology models attempt to mathematically represent the biological system at the molecular level and overlay pathological perturbations. They are similar to what are known as physiologically based models (15). The systems biology model parameters for the various bioprocesses are estimated from multiple experiments, most often in vitro or ex vivo. The observed data are then overlaid on the model predictions for qualification. Model parameters can be further refined by sensitivity analysis or re-estimation for the observed data.

Semimechanistic and empirical models, however, are mostly data driven and do not consider data obtained from related diseases. Semimechanistic disease models simplify the biological system just enough to describe the available data. Typically, parsimony is preferred for such models. Consider diabetes, for instance. Eddy & Schlessinger (16) described a diabetes model with more than 50 model parameters. Jauslin et al. (17) and Krudys et al. (18) reported a semimechanistic model for the same disease. Whereas the semimechanistic model is mainly driven by glucose and HbA1c data, the systems biology model can take into account not only glucose and HbA1c information but other related information such as blood pressure, cardiac output, family history, cholesterol, and smoking status. The outputs of the systems biology model include risks of retinopathy, nephropathy, and neuropathy. The semimechanistic model is limited to the prediction of changes in glucose and HbA1c. **Table 1** compares the two types of models. Both types of models are useful, depending on the question being posed during development. Semimechanistic models are perhaps the first step toward a systems biology model. Perelson et al. (19) proposed an HIV dynamic model. However, this model does not consider the implications for CD4+ levels or the effects of elevated viral load on the incidence of opportunistic infections, or on HIV-related mortality. One of the most important aspects of the systems biology model is the characterization of the relationships between the biomarkers and the clinical outcomes. Another feature that is seldom considered in disease models is the linkage between preclinical and clinical biomarkers. As expected, biomarkers further upstream from the clinical outcome possess less predictive power.

Table 1 Comparison of systems biology, semimechanistic and empirical disease models

Feature	*Systems biology models*	*Semimechanistic models*	*Empirical models*
Source	Underlying biology and individual, detailed experiments	Typically one or more experiments	Typically one or more experiments
Complexity	Very complex	Relatively simple	Relatively simple
Validation	Very challenging	Relatively simple	Relatively simple
Resources	Extremely involved and diverse expertise needed	Less involved and fewer experts needed	Less involved and fewer experts needed
Scope	Flexible; often, inter-relationships with related systems also included	Narrow; do not consider related systems	Narrow; do not consider related systems; might not accommodate variations in experimental designs
Application	Target identification; dose selection; trial design optimization; risk projection based on biomarker data	Dose selection; trial design optimization; go/no-go decisions	Dose selection; trial design optimization; go/no-go decisions

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Empirical disease models bear little resemblance to the underlying biology; they are merely mathematical models to interpolate between observed data. These models are also useful and, in several instances, all that are available. For instance, the relationship between the change in tumor size and survival is typically described using empirical parametric hazard models, yet this empirical model is invaluable in making go/no-go decisions and in designing pivotal trials. Some disease states such as pain and depression are assessed by subjective scores. These diseases might be less amenable to mechanistic modeling. In fact, we believe that every model will necessarily have a few empirical components. The systems biology model for diabetes, although based on physiology, will need to establish the relationship between changes in blood pressure and/or glucose and a myocardial infarction event, which is binary.

Modeling natural disease progression has been a considerable focus of recent research (20). The goal of this component of the disease model is to describe the change in the clinical outcome over time. Holford & Peace described the natural progression of Alzheimer's disease as measured by the Alzheimer's Disease Assessment Scale (ADAS)-Cognitive score (21) using a linear model. The progression of Parkinson disease as reflected by total Unified Parkinson Disease Rating Scale (UPDRS) was modeled by Holford et al. and FDA scientists (22, 23). While these aforementioned models are empirical, more mechanistic disease progress models are being proposed. Earp et al. reported a mechanistic disease progression model for arthritis in rats (24). Mechanistic progression models are more generalizable in that data collected under varied experimental conditions can be analyzed simultaneously.

The third component of the disease model is the placebo effect model. Placebo effect is not, per se, related to the disease, but is a manifestation of a patient's psycho-biological responses (25). Most disease states measured by symptoms have considerable placebo or white-coat effects. Modeling the time course of placebo effects is critical in projecting net drug effects and estimating sample sizes while designing trials. Several researchers have quantified both the magnitude and time course of placebo effects. At the FDA, our obesity trial analysis (23) suggested that patients receiving placebo (with diet and exercise) lost an average of 2.5 kg in approximately 25 weeks. Gomeni & Merlo-Pich (26) developed a Bayesian model for the change in the Hamilton Depression Rating Scale (HAM-D) scores in depression trials. Kowalski et al. (27) recently published a placebo model for acute pain. Placebo effects often depend on the trial design. For example, Su et al. report that Crohn's disease trials with more frequent follow-up visits demonstrate lower placebo responses (28).

Drug Model

Given the numerous research articles on drug or exposure-response [or pharmacokinetic-pharmacodynamic (PKPD)] models, we will not discuss them further here (29, 30). However, in order to decrease the attrition rate in late-phase clinical trials, better early dose-ranging studies are necessary. Early studies that focus on bridging exposure response across patients, healthy subjects, animals, and in vitro results are very important. Wang et al. (9) describe a case study of how bridging exposure response across patients and healthy subjects aided in designing better future trials for a potential drug to treat insomnia.

Exposure-response modeling has previously been oriented toward effectiveness. With the increased use of modeling in the regulatory setting, safety is now more routinely analyzed using exposure-response modeling (31–33). Bhattaram et al. (3) and Garnett et al. (34) describe a few cases where the exposure-safety relationship played a key role in regulatory decision-making. Future work will need to focus on developing early safety markers that are more predictive in the clinical setting. Safety data from late-phase and postmarketing studies are seldom analyzed in

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conjunction with preclinical and early clinical biomarker data. Quantifying safety biomarker and outcome relationships could help to minimize late-phase surprises. The systems biology models described here will greatly enhance our ability to predict long-term safety early in drug development. Regulatory bodies and industry might be able to tailor the level of safety assessments required for a new investigational drug based on early data and model predictions.

Trial Model

In addition to disease and drug properties, a significant portion of the outcome of a trial is determined by patient characteristics and predictable behavior. Inclusion/exclusion criteria, premature discontinuation, and lack of adherence to the protocol or to the prescribed regimen can meaningfully affect trial outcomes. Often, investigators publish the mean and range of the baseline patient characteristics. Unfortunately, the interdependence (covariance) of these baseline variables is not routinely reported. For example, the interdependence of baseline weight and sex, if any, is not evaluated. Reliable simulation of future trials is not feasible without incorporating such knowledge. Our research (23) shows a correlation between baseline body weight and sex and race in obesity trials. Caucasian females weighed an average of 99 kg, while black males weighed 131 kg. Having access to this knowledge is important because the drug effect was proportional to baseline weight. We are unaware of other such models describing the interrelationships among baseline factors in literature. Similarly, dropout rates are often provided as aggregates, and models that describe when and why patients discontinue a trial are not developed. Patients discontinuing a treatment or a trial are providing information that will likely be useful. They discontinue either for completely random reasons or for reasons related to effectiveness or safety. Such information is essential not only for designing better trials, but for optimizing therapeutic value and pharmacoeconomics. Analysis of obesity trials and Parkinson disease trials (23) indicates that patients discontinued owing to negligible weight loss and a worsening of symptoms, respectively. In both cases, at the FDA we modeled the dropout pattern using parametric hazard models. These models can be utilized to simulate dropouts in future trials. Few researchers have discussed the importance of adherence patterns and discontinuation of therapy, particularly in the area of HIV (35, 36). However, these approaches have not been embraced to the fullest extent during drug development even when they are applicable.

The disease-drug-trial models are never complete; they are ever-evolving as new information is made available. But it is possible a given development program might need only some of the aspects of the disease or drug models. For example, in order to design more efficient non–small cell lung cancer (NSCLC) pivotal trials, a reasonable starting point could be to first understand the relationship between tumor size and survival across multiple trials. Extending this relationship to include pharmacologic activity and/or preclinical information could be a subsequent step.

Case Studies

A complete integrated disease, drug, and trial model suite for a given disease has not been published. We believe that the pharmaceutical industry might be building parts of such models for internal use. Summaries of two disease-drug-trial models coming from our experience at the FDA are described below. **Table 2** provides the objectives and description of the various components of the Parkinson and NSCLC disease models. Technical details of these models are not provided here.

Parkinson Disease

Pharmaceutical companies are attempting to develop drugs that can slow the progression of Parkinson disease. This is referred to as disease modification. Currently, there is no U.S. Food and Drug

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Table 2 Description of the Parkinson and non–small cell lung cancer disease-drug-trial models

Feature	*Parkinson disease*	*Non–small cell lung cancer*
Objective	To derive trial design, endpoints, and analysis to support a disease-modification claim	To develop an empirical biomarker-clinical outcome model across drugs
Disease model	Empirical (linear) natural disease progression and placebo models for UPDRS	Tumor progression and tumor size-survival models.
Drug model	Hypothetical disease-modifying drug effects models (only symptomatic drugs approved thus far)	Tumor progression model parameters for each drug estimated separately.
Trial model	Baseline UPDRS and age at onset models; parametric hazard model for patient discontinuation (mainly owing to worsening of symptoms)	Baseline tumor size and patient status (ECOG) models; separate tumor size-survival model for patients with missing data
Scope for expansion	Disease model can be extended to include biomarker(s) effects on UPDRS scores	Mechanistic tumor progression, including effects on other biomarkers and genetic factors
Application	Simulate clinical trials to explore design, endpoint, and analysis options; also can be used to design drug trials for symptomatic relief.	Simulate pivotal trials to make go/no-go decision early in development, project effect sizes and dose selection.

Administration (U.S. FDA)-approved drug that can claim to modify the time course of Parkinson disease. We developed disease-drug-trial models to explore competing trial endpoints and analyses that could discern between a symptomatic and a disease-modifying effect. The main goal of this research was to explore a variety of statistical tests that might be able to discern disease-modifying effects. Only simulations allow controlling for true and false scenarios, and hence were inevitable for this project.

The FDA database included information from nearly 1500 patients with early-stage, idiopathic Parkinson disease. The duration of the trials in the database ranged from six months to three years. This database included both information collected from placebo and active treatment groups in a double-blind treatment phase, as well as long-term open-label follow-up. The proceedings of the Clinical Pharmacology Advisory Committee meeting (23) include a detailed description of the model and the simulation results. Models for the natural progression of Parkinson disease, drug effects, baseline demographics and patient discontinuation were developed. These models were used to simulate a two-phase study design (delay-start) to assess the false-positive rate and power for various endpoints. Divergent slopes in the first phase between placebo and active treatment, followed by a demonstration of reasonably constant difference between the two active treatment arms in the second phase, could constitute reliable evidence of effectiveness.

NSCLC

Lung cancer had the highest cancer-related death rate during the past decade, exceeding that of colon, breast, and prostate cancer combined. Despite a significant unmet medical need for new cancer treatments, anticancer drugs have one of the lowest rates of successful drug development at only 5% (37). Even compounds reaching Phase III clinical trials have a failure rate of about 60%. At the FDA we developed a tumor size (i.e., biomarker) and survival (i.e., clinical outcome) model utilizing data from across a number of NSCLC trials (see below). We believe this model can facilitate clinical screening of novel compounds and provides a tool that drug developers can use to perform clinical trial simulations to improve the design of future trials.

Four drug registration trials for NSCLC containing nine different treatments were utilized to develop pharmaco-statistical models that link survival to baseline risk factors and changes in

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tumor size during treatment. The purpose of these models is to leverage prior quantitative knowledge to facilitate future drug development of other NSCLC regimens. Eleven risk factors were screened based on a Cox proportional hazard model. Tumor size dynamics were modeled with a mixed exponential decay (i.e., shrinkage) and linear growth (i.e., progression) model to estimate tumor sizes of individual patients over time. Survival times were described with a parametric survival model that included the key risk factors and tumor size change as predictors. Eastern Cooperative Oncology Group (ECOG) score and baseline tumor size were consistent prognostic factors for survival. Changes in individual patients' tumors were well described by the mixed shrinkage/progression model, especially during early weeks after treatment initiation. The parametric survival model included the ECOG score, baseline tumor size, and week-eight tumor size change as significant predictors for patient survival time. The survival model developed from one treatment group predicted the survival outcomes for the other eight treatment groups, despite the different mechanisms of action and the fact that they were studied in different trials. Tumor size change at week eight, when incorporated into the parametric model, allows early assessment of activity of an experimental NSCLC regimen. The survival model and the tumor dynamic model will be beneficial for screening early clinical development candidates, simulating NSCLC clinical trials, and optimizing trial designs. The proceedings of the Clinical Pharmacology Advisory Committee meeting (38) include a detailed description of the model and the simulation results.

SUMMARY POINTS

1. One key first step for the industrialization of disease-drug-trial model building and application is to consider the initiative as critical to the success of drug development (i.e., to view it as important as the primary analysis of a clinical trial). Realization of the value of these models can occur only through publicly and increasingly sharing the success stories.
2. Various methodologies to develop disease-drug-trial models are available. However, these analyses are extremely time consuming and require diverse experts to work together. Industry and regulatory processes are currently not organized to accommodate such collaborative research. A potential solution could be public-private partnerships to achieve common goals.
3. A challenge related to the above is the lack of an adequate number of trained scientists to perform such work. Disease-drug-trial models fall under applied research and few federal grants are targeted to such projects. The primary stakeholders for these models are the pharmaceutical industry and patients. The pharmaceutical industry should greatly increase their support to academic institutions to develop these models and train more quantitative scientists. Patient advocacy groups should support academic and regulatory institutions that conduct such research. Professional scientific organizations also can contribute and facilitate the research.
4. Standards for data submission and infrastructure that allow ready access to prior data are lacking. Currently at the FDA, analysis data sets for modeling are derived from data submitted by pharmacometricians in industry. Unfortunately, different industry sponsors follow different data specifications. Both industry and the FDA will need to accept fundamental changes in how data (information) and models (knowledge) are managed and made available to scientists. Implementation of the Clinical Data Interchange Standards Consortium (CDISC) (**http://www.cdisc.org**) standards for regulatory submissions may help to streamline the data specifications. Next, tools will need to be developed to extract

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these data and generate analysis data sets at the click of a button to allow ready access of important data to modelers. Finally, the modeling results will need to be archived in a manner that is transparent and retrievable by others.

5. Another challenge with respect to tools is the absence of a software suite to perform the different steps in a modeling and simulation project that increase the ease and efficiency of analyses. Data formatting, modeling, simulation, visualization, and archiving currently cannot be performed using one particular software program. More versatile software packages are needed to alleviate this inconvenience and inefficiency. Scientists should use new software as it becomes available to explore and support innovation. The FDA is certainly open to usage of new modeling and simulation software.
6. Validation presents a specific challenge with the systems biology disease models. To date, most of these models are black boxes and the model details are not published. Even if one gains access, it might be very challenging to validate these complex models, which are developed over several years. As a result, users will be uncomfortable accepting and using these models; thus, there is a need for developing criteria for acceptance.

FUTURE ISSUES

The Pharmacometrics group within the Office of Clinical Pharmacology has been fostering disease-drug-trial models within the FDA to aid regulatory and drug development decisions. Several of the contributions are discussed here and references for others are provided. The following is our vision with respect to these models:

1. Given the limited resources, consortia on focused topics would be an effective approach to developing these models. The Predictive Safety Testing Consortium (PSTC) (**http://www.c-path.org/Portals/0/PSTC%20Overview.pdf**) is one example of such a consortium.
2. The main focus of our work at the FDA will continue to be in the area of semimechanistic disease-drug-trial models. We intend to launch a public website to share our model library. Our group will continue to publish its results in scientific journals.
3. The disease-drug-trial models, as they become available, will be employed to design pediatric trials using clinical trial simulations. Our target is to design 50% of all pediatric trials using clinical trial simulations by 2015 and 100% by 2020. Industry will need to play an important role in this initiative.
4. As adequate experience is gained with a particular disease-drug-trial suite, we intend to standardize the data and analysis submission specifications. Our goal is to develop standard templates for 15 therapeutic indications by 2020. These 15 therapeutic areas will be selected based on public health priority, prior experience, and richness of the pipeline.
5. As the systems biology disease models are very complex and typical validation methods do not apply, there is a need for building criteria for evaluating these models to allow more usage. The FDA can actively participate with other experts in developing such guidelines.

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6. We envision training 20 pharmacometrics scientists by 2020. Creating disease-drug-trial models could be an excellent goal for such fellowships. Academic and research institutions can lead a few of these fellowships.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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