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Challenges in the Transition to Model-Based Development

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ABSTRACT

Practitioners of the art and science of pharmacometrics are well aware of the considerable effort required to successfully complete modeling and simulation activities for drug development programs. This is particularly true because of the current, ad hoc implementation wherein modeling and simulation activities are piggybacked onto traditional development programs. This effort, coupled with the failure to explicitly design development programs around modeling and simulation, will continue to be an important obstacle to the successful transition to model-based drug development. Challenges with timely data availability, high data discard rates, delays in completing modeling and simulation activities, and resistance of development teams to the use of modeling and simulation in decision making are all symptoms of an immature process capability for performing modeling and simulation.

A process that will fulfill the promise of model-based development will require the development and deployment of three critical elements. The first is the infrastructure—the data definitions and assembly processes that will allow efficient pooling of data across trials and development programs. The second is the process itself—developing guidelines for deciding when and where modeling and simulation should be applied and the criteria for assessing performance and impact. The third element concerns the organization and culture—the establishment of truly integrated, multidisciplinary, and multiorganizational development teams trained in the use of modeling and simulation in decision-making. Creating these capabilities, infrastructure, and incentivizations are critical to realizing the full value of modeling and simulation in drug development.

KEYWORDS: pharmacometrics, model-based development, real-time data assembly

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PERSONAL REFLECTIONS

During my 2-year clinical pharmacology fellowship with Dr. Leinis Sheiner at the University of California, San Francisco, starting in 1980, my primary research project focused on an evaluation of the population pharmacokinetics (PKs) of procainamide and its metabolite, *N*-acetyl procainamide, using plasma samples left over from routine laboratory evaluations and timed urine collections in patients treated for arrhythmias.¹ My experiences in one of the earliest applications of nonlinear mixed-effect modeling (NONMEM) left an indelible impression as to the potential value of population modeling, as well as the difficulties in successfully executing a population analysis.

The project required that I keypunch data onto cards and submit the NONMEM runs via a card reader to access the Lawrence Livermore Laboratory mainframe. The NONMEM Project Group had its research account on this mainframe, and Dr. Stuart Beal was responsible for monitoring expenditures for mainframe time. To conserve resources, I was asked to carefully select runs for submission and to submit jobs after 9:00 PM, when cheaper computing rates applied. Parsimony proved to be a difficult principle to adhere to, because punching data onto cards often resulted in inadvertent mistakes that were not detected until the run ended in errors. Needless to say, the frequent rerunning of data and attendant incurred charges were not lost on Dr. Beal.

At the time, NONMEM users were required to write their own prediction subroutine (PRED) to generate the predictions of drug concentrations at the time of the measured values. The procainamide model involved plasma and urine measurements of both procainamide and *N*-acetyl procainamide. The predictive equations had to be written in recursive formats that were then used to compute the analytic form of the partial derivatives. The entry of the equations into the program to compute the partial derivatives and the subsequent hand entry of the derivatives onto punch cards was also fraught with errors. I believe that these trials and tribulations are some of the reasons why we now have PRED PP (PRED Subroutine for Population Pharmacokinetics).²

Many of the technical aspects of the application of mixed-effect modeling in the analysis of PK and pharmacody-

namics (PD) data have improved tremendously over the last 20 years. Other aspects have not changed, and these obstacles represent frequent sources of frustration for scientists seeking to use modeling and simulation to inform drug development and regulatory decision-making. This article describes the nature of the important obstacles that must be resolved if modeling and simulation is to have maximal impact on drug development.

INTRODUCTION

The application of population approaches to the investigation of PKs and PDs has had an important impact on drug development. The role of mixed-effect modeling has grown from early investigations of population PKs in patients enrolled in clinical trials and the evaluation of covariates as sources of PK variability to the development of PK and PD models that provide a comprehensive, exposure-response-based characterization of safety and efficacy.

Technically, the process for estimating population PK/PD parameters using mixed-effect modeling has improved dramatically since it was first proposed by Sheiner and Beal.² The development of PRED PP, the growing body of examples of mixed-effect modeling applied to specific therapeutic areas, and the availability of fast and cheap computer resources are all important milestones. These advances, along with the growing recognition of the value of modeling and simulation in drug development, have all helped to contribute to the expanding list of development programs that have successfully used modeling and simulation in decision making.

Practitioners of the art and science of pharmacometrics are well aware of the considerable effort required to successfully complete modeling and simulation for drug development programs. This is particularly true because of the current, ad hoc implementation, wherein modeling and simulation activities are piggybacked onto traditional development programs. The process used for implementing modeling and simulation has evolved over time, and pharmacometricians are at an important disadvantage as we move toward model-based development, because this process has not been explicitly designed to address critical success factors.

This paper focuses on two theses. The first thesis is that modeling and simulation will play an increasingly important role in drug development and that this role will shift over time from a supportive function in the current empiric-based development paradigm to a central role in a fully model-based development paradigm. The second thesis is that the design, deployment, and maintenance of a reliable and efficient process for pharmacometric analysis represents a critical challenge that must be addressed if the full value of modeling and simulation, even in a supportive role, is to be realized.

A CHANGING DEVELOPMENT PARADIGM

The 1962 amendment to the Federal Pure Food, Drug, and Cosmetic Act requires that manufacturers demonstrate the safety and effectiveness of their products by conducting adequate and well-controlled studies. The empiric-based development paradigm that has evolved from this mandate has been a powerful tool for assuring the safety and effectiveness of marketed products. The randomized, double-blind trial represents a clear and unambiguous standard for demonstrating efficacy and provides the basis for a binary yes or no approval decision during the review of study results by regulatory agencies.

More recently, there have been growing concerns regarding the rising costs of development and reduced pipeline productivity. A recent Food and Drug Administration (FDA) report states that new compounds entering phase I have an 8% chance of reaching the market place today versus a 14% chance 15 years ago. Additionally, the phase III failure rate is now reported to be 50% versus 20% from 10 years ago. In the view of the FDA, this falling success rate has occurred because the applied sciences needs for medical product development have not kept pace with the tremendous advances in the basic sciences. The new science is not being used to guide the technology development process in the same way that it is accelerating the technology discovery process.³

At the same time, there has also been increased scrutiny of the ability of the FDA to certify the safety of new medicines. A number of drugs have been withdrawn from the marketplace or required significant changes in the product label because of drug safety concerns uncovered after marketing.

The inviolable requirement to demonstrate the safety and effectiveness of new medicines coupled with the critical business challenge of dealing with rising development costs and an increased risk of failure is creating a “perfect storm” in the pharmaceutical industry. These challenges have placed increased pressure on the industry and regulatory agencies to find new approaches to drug development. The FDA has recently called for the implementation of a Critical Path Initiative to develop and deploy “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.”³ One aspect of this initiative calls for the transition to a more model-based development approach based on the learn-and-confirm paradigm proposed by Sheiner.⁴

The application of the learn-and-confirm paradigm breaks development into 2 major learn–confirm cycles. In the first cycle of phases I and IIa, we learn what dose is tolerated in normal subjects and subsequently confirm that this dose has the potential to be effective in selected patients. At the

end of phase IIa, we reach a decision point as to whether there is sufficient evidence of efficacy and a corresponding lack of toxicity to justify additional investment. If so, the second learn–confirm cycle of phases IIb and III/IV is begun. The goal of the learning step of phase IIb is to learn how to use the drug in representative patients to improve the odds of an acceptable benefit-risk assessment. The goal of the confirm step (phase III/IV) is to demonstrate, in a large and representative patient population, that an acceptable benefit/risk profile has been achieved.

This paradigm relies on the application of modeling and simulation to assist in the transition through the learn–confirm cycles. We incorporate the knowledge from one step of development in an explicitly specified model and formulate how the next step in development is to be performed. For example, the end-of-phase IIa meetings between sponsors and FDA allows for the review of all of the available information in support of the dose for later-stage development. Modeling of preclinical and early clinical data and extrapolation of results via simulations to the design and expected outcomes of phase III clinical trials have become an important basis for decision making at these meetings.

The real difference between empiric-based development and model-based development is the role that models play in the process of hypothesis formulation and confirmation. In the current model-supported, empiric-based paradigm, modeling and simulation play supportive roles in helping to set the design characteristics of empirical clinical trials. In a fully realized model-based development paradigm, models will be both the instruments and aims of drug development programs. There is a much more intimate relationship among the premises, hypotheses, and theorems that a model realizes or conveys, on the one hand, and those that a clinical trial is meant to test. In other words, the model-based paradigm will focus on the development and support of models as the primary outcome of a development program. This entails a much more iterative process that is currently used and the need for a much more rigorous and efficient “industrialized” process to support timely decision-making.

PHARMACOMETRICS IN A MODEL-SUPPORTED PARADIGM

In the current business and regulatory climate, modeling and simulation will likely continue to grow in importance as a supportive function. But even in this supportive role, the successful application of modeling and simulation must be accompanied by critical strategic, logistic, tactical, and architectural infrastructure advances. The lack of these critical infrastructure elements is a major impediment in the successful deployment and sustainment of modeling and simulation in drug development.

It is useful to examine the reasons why the execution of traditional clinical trials within the empiric-based development paradigm has been so successful. From an architectural perspective, the entire process of clinical trial execution including study design, data collection, data scrubbing, data management, data programming, analysis, and reporting is geared toward maximizing the efficiency, cost, and schedule requirements of the empiric-based paradigm. The design principles of clinical trials are well understood, and textbooks with prototypical development strategies are available to guide programmatics. The time and resource requirements are well appreciated, and the informatic elements are straightforward and relatively easy to acquire. Consequently, the production of analysis results is predictable in both cost and schedule. The process is reliable, repeatable, and determinable. Once the analysis plan has been specified, data analysis programs can be written and verified during data collection so that results can be readily generated once database lock has been accomplished. Importantly, the outcome of the process, the *p* value, is adequate for the purposes of the major stakeholders, including regulatory agencies, development and marketing teams, and even prescribers. These characteristics serve as baseline performance measures that any new paradigm, including one supported by modeling and simulation, must exhibit.

Model-supported development, as it is currently implemented, shares few of these critical programmatic characteristics. There are important data availability and quality issues that contribute to highly variable costs and schedule requirements for PK/PD model development and analysis activities. The process of performing a model-based analysis is model-dependent and analyst-dependent. The process is nonprogrammatic because model-based development is both a “hypothesis generator” and a confirmator. Importantly, the outcomes of the analyses are interpretable in different ways by different stakeholders and are overly complex for historical stakeholder purposes. There is no textbook that provides rigorous and well-accepted principles for the design, implementation, and interpretation of a model-based development program.

The lack of explicitly designed programmatics and processes for modeling and simulation has placed enormous pressure on pharmacometricians to deliver results in a time frame that corresponds with the delivery of traditional statistical analyses, often defined as within 14 days of database lock. The overall time frame for a typical exposure-response evaluation, encompassing a variety of modeling and simulation activities, can be weeks or months depending on the complexity of the analysis. Figure 1 is a pie chart showing the relative proportion of time required for the typical activities involved in an exposure-response evaluation based on our collective experiences.⁵

Figure 1. Pie chart showing the relative proportion of time required for the typical activities involved in an exposure-response evaluation. The overall time frame for an exposure-response evaluation encompassing these activities can be weeks to months depending on the complexity of the program. Based on data on file at Cognigen Corporation.

If modeling and simulation results are to be delivered in a timely manner so that they can inform development and regulatory decision making, the industry must move beyond ad hoc implementation and address infrastructure, process, organizational, and culture issues with the same consistency and efficiency currently attendant with empiric-based development. These issues bear on data assembly, modeling and simulation activities, and communication strategies used by pharmacometricians.

Data Assembly

The lead time required for development of population PK models and the performance of exposure-response modeling places enormous pressure on data management to expedite data scrubbing and dataset assembly so that modeling and simulation efforts can be initiated as quickly as possible. The assembly of datasets for a population PK/PD analysis is complicated by the complexity of both the content and the structure of the required database. These analyses typically required pooling disparate data, including PK information, the drug dosing history, patient demography, laboratory data, concomitant medicines, and measures of efficacy and safety to create a time-ordered sequence of relevant events for each patient from the time of enrollment in a trial until its conclusion.

This information must be secured from numerous databases managed by different functional groups, either internal or external to the company, so accessing and pooling the data can be cumbersome and time consuming. Moreover, the definition data are inadequate to support efficiencies in the assembly process, which generally entails a manual process dependent on the skills of the data manager.

Once the data are pooled, a myriad of problems can be encountered during data scrubbing. A number of essential data queries, particularly the determination of whether the drug concentration values and the date and time of sampling make sense in the context of the dosing history, cannot be performed until the drug concentration database is merged with the drug-dosing history for each patient. Yet, it is common for these individual data elements to be queried separately, so the important questions as to whether data issues will impact on the quality of the results or preclude any meaningful analysis may not be recognized in a timely manner.⁶

Data assembly and querying procedures performed for one recent study resulted in a 50% discard rate of the concentrations because of recording errors in sampling and dosing time, incomplete data collection, and administrative errors noted after merging the drug concentration and dosing history databases. The time and expense associated with discarded drug concentrations underscore the need for a commitment to specialized monitoring for clinical trials incorporating sparse sampling for mixed-effect modeling. This effort in itself can be costly and time consuming, but experience has shown that it is required to ensure the quality of the results.⁷

Ideally, PK data should be queried during trial execution to identify problems early so that they can be rectified by appropriate interventions at the problem sites. Our experiences in developing a process for real-time data assembly during the delavirdine phase III clinical development program are illustrative of the issues that arise and the value provided by this strategy.⁸

Delavirdine Case Study

Delavirdine mesylate is a nonnucleoside reverse-transcriptase inhibitor that is currently approved for the treatment of HIV infection. During the design of the phase III development program, concerns over potential safety issues associated with saturable metabolism prompted the sponsor to initiate a program to monitor drug concentrations in all of the patients who enrolled in two double-blind, randomized, pivotal registration trials to allow dosing adjustments in patients who were experiencing elevated concentrations of delavirdine.⁸

Maintaining the study blind was an important issue with respect to the data assembly and concentration monitoring program. The procedures for maintaining the study blind started with very strict conservative reporting standards. Patient-specific information was presented with a blinded identification number, and data summaries were only presented if the sample size was larger than a predetermined number for each display. Contacts to blinded study

personnel were scripted to minimize the chance of inadvertent disclosures that would compromise study blind. In the event that a dosage adjustment was required for a patient, another patient who was randomized to the placebo was also identified, and a similar, mock-dosage adjustment was made.

The delavirdine sparse concentration time data collected during the regular clinical visits were subsequently combined with information regarding demography, delavirdine dosing history, concomitant medications, adverse events, and laboratory safety studies. The data assembly process allowed for the expedited scrubbing of the drug concentration time data along with the corresponding dosing histories and facilitated monitoring of possible concentration-related safety events and screens for drug-drug interactions during the trial. This information was then used to prepare summary reports that were submitted to the data safety monitoring board. The compliance of each site with respect to protocol requirements was monitored, and sites received feedback to improve compliance. This evaluation also served to identify and censor sites failing to meet the minimum criteria for data validity and reliability.

This program had an important impact on patient recruitment and safety monitoring. Patients who might have been excluded based on concomitant medications were included, enhancing recruitment, and patients subsequently found to have low exposures to delavirdine because of concomitant use of metabolic inducers were identified and discontinued their study participation, addressing an important ethical issue. In addition, the data assembly process allowed for a much more efficient and timely completion of modeling and simulation activities and the preparation of supportive material for the regulatory submission. The value of real-time data assembly was subsequently recognized in the FDA Guidance on Population Pharmacokinetics.⁹

The Modeling and Simulation Process

When first introduced into drug development, mixed-effect modeling of sparse samples focused on estimating the population PK parameters of a drug. The goal was generally to assess the influence of patient covariates, such as demography, laboratory data, and concomitant medications, on the typical values of PK parameters and the magnitude of interindividual and intraindividual variability. Although this is still a common component of population analysis, the focus of mixed-effect modeling for the purposes of decision-making has shifted to the estimation of patient-specific measures of exposure and the incorporation of these estimates into exposure-response evaluations. These evaluations provide an assessment of the clinical importance of altered PK disposition and allow a more detailed

Figure 2. Tasks and timelines for modeling and simulation activities superimposed on a linear development strategy. This implementation is often required to compensate for management requirements that exploratory development be completed rapidly so that a go/no-go decision for full development can be made as soon as possible.

assessment of the determinants of efficacy and safety outcomes. This assessment is one of the key value propositions of model-supported development.

Often the reason given for obtaining sparse samples in a clinical trial is as an insurance policy in the event that the study results are not as expected. In this situation, the thought is that a subsequent exposure-response analysis may offer an explanation for the findings and point the way forward. This has created a chicken and egg conundrum, because the inadequate attention to sampling design and data management coupled with the need to urgently perform retrospectively designed analyses has limited the value of modeling and simulation in decision-making. Analyses conducted under these conditions may provide insights of value for the immediate need, but they often reveal the possibility of more important insights that cannot be additionally explored because of inadequate designs or data management procedures.

Because of the long lead time for modeling and simulation activities, some pharmacometricians have been successful at moving the development teams toward a more deliberate and proactive implementation plan. Figure 2 shows the tasks and timelines for modeling and simulation activities superimposed on a linear development paradigm. This commonly used strategy is focused on rapidly completing the exploratory development so that a “go/no-go” decision for full development can be made as soon as possible.

As the popularity of modeling and simulation increases, pharmacometricians are going to be faced with the task of triaging development programs to the appropriate application of modeling and simulation. We must deal with questions such as how do we decide when and where modeling and simulation should be applied? How do we assess the

performance and impact of modeling and simulation? From a technical perspective, experienced modelers have been proficient at dealing with the vagaries of population analysis, and sophisticated models can be readily specified with the tools available in NONMEM. But there is little formal guidance in determining when an analysis has been completed to an acceptable level of quality. These problems are going to become even more acute if we move toward a full implementation of model-based development as described below.

Communications

An important challenge in communicating the results of modeling and simulation activities to the development team is often the general lack of familiarity by the team with the results and the difficulty in making decisions on results that are not reducible to a *P* value. The principal stakeholders in the drug development process, particularly the development team, the regulatory review team, and the marketing group, have come to expect and make decisions on a binary outcome of a clinical trial as provided by the *P* value-driven concept of efficacy and safety. Thus, the outcome of modeling and simulation is overly complex, because it describes a continuum of outcomes and decisions that must focus on setting threshold values that then have important downstream implications.

The aggressive timelines for development and the importance of meeting milestone decision points has led to an assembly line mentality to generating analysis results and technical reports. Consider the analysis of drug concentration data collected during a traditional PK study. These data are typically analyzed using noncompartmental methods, and the process of performing the analysis and generating the report is nearly completely automated with commercially available software. Executive summaries of the results are then distributed to globally distributed team members as a PowerPoint presentation via email.

This straightforward communication strategy has spawned expectations for a similarly straightforward presentation of population PK/PD analyses. As a result, the members of the development team can be overwhelmed by the complexity of the results. This complexity can be compounded if the teams are subjected to a debate among the members of the pharmacometrics group as to the relative value of a 2-compartment versus a 3-compartment model in improving the goodness-of-fit plots. Pharmacometricians must recognize that the main challenge of the development team is to integrate emerging information on safety and efficacy into decisions on whether and how to continue with the development program. The strategic importance of modeling and simulation results in this decision-making process must be emphasized in presentations to the development

team, predicated on the pharmacometrician's scientific assessment as to the underlying appropriateness of the model. This latter conclusion is best challenged and defended in presentations to peers in the pharmacometrics group where the emphasis is on the quality of the fit and the appropriateness of decisions made during the modeling fitting process.

There is an additional complicating reality in the current implementation of modeling and simulation. There can be discrepancies between the information provided by modeling and simulation and other sources of information that serve as a basis for decision making by the team. Consider the frequently encountered scenario in which a team leader with an underlying resistance to the use of modeling and simulation is faced with conflicting information and an urgent-decision milestone deadline. In this scenario, modeling and simulation results may be ignored, perhaps at the peril of the compound and company.

These same challenges in educating the development team must often also be addressed during interactions with the review team at regulatory agencies. The end-of-phase IIa meetings with the FDA, with their emphasis on dose justification, have been excellent forums for presenting modeling and simulation results, discussing the technical aspects of the analyses, and considering their implications. As the development programs progress, however, discussions of new modeling and simulation results are generally held in the context of sponsor-FDA meetings where the agenda may be dominated by more urgent clinical issues. These meetings allow little time for pharmacometricians on both sides to have meaningful discussions of the technical aspects of the analysis. Modeling issues may not get addressed and reconciled until after the regulatory filing when it may be too late to address reviewer concerns in a meaningful way. This problem is additionally compounded by the lack of objective measures to judge the quality of an analysis, lack of formal agreement on the content and format of reports, and a lack of an a priori agreement over the regulatory implications of modeling and simulation results. This lack of agreement can be the source of ambiguity as to the requirement to perform a follow-up study to confirm an observation from the population PK/PD analysis. Curiously, some teams still express their resistance to using modeling and simulation in development by citing concerns about the marketing implications of a therapeutic drug-monitoring requirement if an exposure-response relationship is detected.

PHARMACOMETRICS IN MODEL-BASED DEVELOPMENT

The linear implementation paradigm for modeling and simulation described in Figure 2 is already being replaced with a more iterative strategy for generating early informa-

Figure 3. Development teams are beginning to rely on small proof-of-concept (POC) studies that yield critical strategic insights on a candidate drug. The evolving insights from the POC studies are then evaluated against the desirable target product profile to continually update the clinical and commercial potential of the candidate.

tion about the potential of a new medicine. Development teams are beginning to rely on small proof-of-concept studies that yield critical strategic insights on a candidate drug. As illustrated in Figure 3, the evolving insights from the proof-of-concept studies can then be evaluated against the desirable target product profile to continually update the clinical and commercial potential of the candidate drug.

This paradigm is even more dependent on modeling and simulation and, consequently, places more stress on pharmacometricians and the development infrastructure. One of the key challenges will be the development of accurate and generally accepted methods for determining the values of key attributes and efficiently computing up-to-date “value” estimates. Not all of the attributes will be of equal weight, and a balance of attributes will be required for cogent decision-making, so working these into a “formal model” will be one of the challenges that must be addressed.

One can envision the creation of a highly integrated “meta-model” that can incorporate data from various experiments and clinical trials to project downstream implications while informing upstream relationships. This model will incorporate components that are important to all of the principal stakeholders, including preclinical, PK, PD, safety, and efficacy outcomes; economic implications; and other attributes that are not well accounted for in the current empiric paradigm to compute the value of a new medicines. This value calculation would then serve as the basis for all of the clinical and business decisions with respect to regulatory approval and commercialization.

This paradigm of drug development will require considerable effort to identify the relevant attributes, develop an acceptable method for computing value, and the specification of acceptable thresholds for decision making. Because

knowledge is accumulated during development, the value estimates will be continually updated and formally incorporated into the decision-making process. From a business perspective, the evolving value of a medicine can be used as a basis for updating expected price, reimbursements, sales, and return on the investment.

An example of the current approach to valuing new medicines reveals some of the deficiencies of the current paradigm and the inherent opportunities in a true model-based development approach. The value of a new biotechnology is often conceptualized as being dependent on future revenue from the final approved product, the cost and time needed to get the product to market, and the various risks along the way. Valuations are commonly computed using the risk-adjusted net present value of the medicine.¹⁰ In this calculation, clinical development is viewed as a series of high-risk wagers. The probabilities of successfully transitioning through the various stages of drug development are estimated, and the value for the wager series is determined by the risk-adjusted payoff and ante. Although commonly used for corporate portfolio management, the risk-adjusted, net present value has important inadequacies. Its computation requires information on clinical success rates, projected costs, the size of the projected market, and the discount rate. The origin of these variables is often based on intuition, and there are problems in properly quantifying the evolving risks of development as new information is generated. Risk-adjusted net present value has no value as a “design to” metric that can be used to quantify gaps and opportunities against the target product profile. Finally, there is no mechanism for incorporating the impact of emerging information on the value and sales of a new medicine.

The industry embrace of the “blockbuster” business model and the emphasis on a binary decision-making process at the FDA also has had important implications for communication to downstream stakeholders including physicians and patients, indeed, the entire health care delivery system. The full implementation of a model-based development paradigm will require a strategy for incentivizing the establishment of truly integrated, multidisciplinary, and multiorganizational development teams. These teams must include representatives from all of the principal stakeholders, representing all of the scientific disciplines involved in the drug development and commercialization enterprise, as well as the health care delivery system.

SUMMARY

The level of effort required to successfully inform development decision making with modeling and simulation results, coupled with the failure to explicitly design development programs around modeling and simulation, will

continue to be an important obstacle to the successful deployment of model-supported development. Data assembly and scrubbing are remarkably time consuming and can result in high discard rates and delays in completing modeling and simulation activities. There is often a resistance to the use of modeling and simulation in decision-making, because the results are not reducible to *P* values, and the opportunities for collaboration on the strategic importance of the results may be sacrificed because of the urgent time frames. These challenges can result in lost opportunities to impact on development and regulatory decision-making and represent symptoms of an immature process capability for performing modeling and simulation.

A mature model-based development process will require the development and deployment of 3 critical elements. The first is the infrastructure—the data definitions and assembly processes that will allow efficient pooling of data across trials and development programs. The second is the process itself—developing guidelines for deciding when and where modeling and simulation should be applied and criteria for assessing the performance and impact of modeling and simulation. The third element concerns the organization and culture—the establishment of truly integrated, multidisciplinary, and multiorganizational development teams trained in the use of modeling and simulation in decision-making. Creating these capabilities, infrastructure, and incentivizations are critical to realizing the full value of modeling and simulation in drug development.

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