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Physiologically Based Pharmacokinetics in Drug Development and Regulatory Science: A Workshop Report (Georgetown University, Washington, DC, May 29-30, 2002)

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ABSTRACT

A 2-day workshop on "Physiologically Based Pharmacokinetics (PBPK) in Drug Development and Regulatory Science" came to a successful conclusion on May 30, 2002, in Washington, DC. More than 120 international participants from the environmental and predominantly pharmaceutical industries, Food and Drug Administration (FDA), and universities attended this workshop, organized by the Center for Drug Development Science, Georgetown University, Washington, DC. The first of its kind specifically devoted to the subject, this intensive workshop, comprising 7 plenary presentations and 10 breakout sessions addressed 2 major objectives: (1) to "define demonstrated and potential contributions of PBPK in drug development and regulatory science," and (2) to "assess current PBPK methodologies with the identification of their limitations and outstanding issues." This report summarizes the presentations and recommendations that emerged from the workshop, while providing key references, software, and PBPK data sources in the appendices. The first day was initially devoted to presentations setting the stage and providing demonstrated applications to date. This was followed by breakout sessions that considered further opportunities and limitations, and which extended into Day 2 to deal with developments in methodologies and tools. Although the primary emphasis was on pharmacokinetics, consideration was also given to its integration specifically with mechanism-based pharmacodynamics.

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INTRODUCTION

Impetus for the Workshop

Although certain physiological aspects of disposition of substances by organs within the body had received attention earlier, it was in 1937, with the seminal work of Teorell, that an integrated approach to whole body physiologically based modeling of pharmacokinetics received first serious attention. However, owing to the resultant mathematical and computational complexities and the lack of some basic physiological information at the time, whole body physiological based pharmacokinetics (PBPK) did not become of age until the 1960s, when, with the aid of the digital computer, modeling contributions from the chemical engineering community reawakened interest in this area. Since then, there have been numerous applications of the approach to a wide variety of chemical and drug substances, varying from small to large molecules, as well as investigations with environmental compounds. Compared, for example, to the sum of exponentials modeling, which is purely descriptive of the observed behavior of the substance under investigation, whole body PBPK modeling provides a mechanistic and more realistic description of the behavior of the substance in various tissues, with the intent of addressing such questions as: Why do we see the observed behavior? Can we explain differences among compounds? Can we better predict pharmacokinetics in human from in vitro and preclinical information and provide increasingly confident predictions of events occurring with drugs at target and other sites (which are rarely directly observable in humans), with age, in disease, and when co-administered with other drugs.

When planning the workshop, the organizers were intrigued that whereas PBPK modeling has become relatively well accepted in the field of risk assessment by the chemical industry and environmental protection agencies, its pharmaceutical application has remained relatively academic to date with little obvious general appli-

cation by industry and in regulatory submissions. Yet, there is an increasing impetus for the use of PBPK modeling within industry driven in part by the desire to make more efficient and informed selection of compounds for development from the myriad coming out of combinatorial chemistry and high throughput biological screens, and in part from the general increasing acceptance of modeling in drug discovery and development as witnessed, for example, in the widening use in clinical trial design and simulation. Moreover, an increasing body of physiological, biological, and pharmacological data has become available over the years to inform PBPK modeling. Collectively, these factors created the impetus for, and suggested the timeliness of, the workshop.

PHILOSOPHY OF PBPK MODELS

Model Structure

Data analysis using empirical models, such as sum of exponentials or compartmental models, implies that a "model" is fit to the experimental data. It is thus the data alone that define the complexity of the structural model. This empirical model is used primarily to describe and interpolate rather than explain observations. In contrast, the philosophy behind whole body PBPK is the overlay of drug specific data onto an essentially independent structural model (Figure 1), comprising the tissues and organs of the body with each perfused by and connected via the vascular system. The independent physiological data comprise, among others, tissue structure, tissue volume, tissue composition, and associated blood flows—all anatomically correct. An attractive feature of the model is that its structure is essentially common to all mammalian species, thereby facilitating interspecies scaling. In addition, as relevant knowledge of the physiological and morphological data becomes available, as well as how drugs interact with the components of the system, the possibility exists for efficient use of limited drug-specific data in order to make reasonably accurate predictions as to the pharmacokinetics of specific compounds, both within and between species, as well as under a variety of conditions.

The PBPK model may exhibit different degrees of complexity and, in its simplest form, it is reduced to its steady-state behavior characterized by such parameters as clearance and volume of distribution. The drug-specific data include tissue affinity, plasma protein binding, and membrane permeability, as well as enzymatic and transporter activity. As a consequence, whole body PBPK models are highly mechanistic in nature, accounting for the causal basis of the observed data. In addition to describing observations in blood taken from a peripheral vein, the usual site to evaluate the pharmacokinetics of a compound, a PBPK model facilitates virtual "visualization" of events at various sites and tissues within the body.

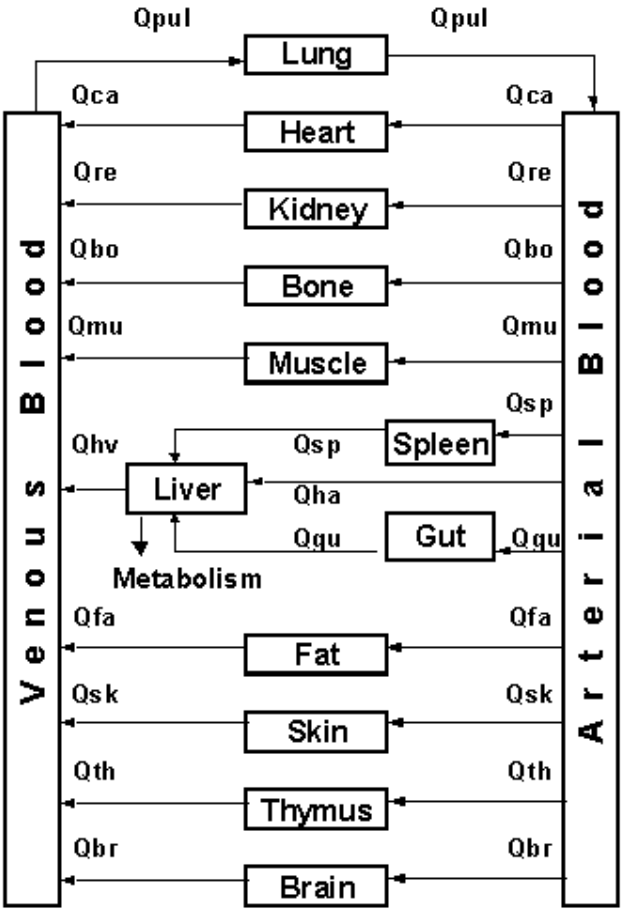

Figure 1. A typical whole body physiologically based pharmacokinetic model. The tissues and organs of the body are arranged anatomically and connected via the vascular system, with Q denoting blood flow.

Model-Building Strategies

Various strategies have been used when implementing whole body PBPK models. As discussed below, it is important to distinguish between model building for simulation from that for data analysis. In the latter case, parameter identifiability is a crucial element of the process. Debates on model structure are ongoing between the "complicators" (ie, those wishing to retain as much of the higher level structure of the global model as possible) and the "KISsers" (those wishing to "**k**eep **i**t [the model] as **s**imple as possible," through lumping of various tissues together). Whatever the case, the modeling process and, implicitly the complexity of the model it-

self, are best undertaken with an eye to the intended application. In practice, this may vary during drug discovery and development as more data become available (such as tissue levels obtained during safety assessment); hence, it is very important to be flexible in the approach. Moreover, if model reduction is employed, it should be undertaken in a formal and systematic way—rather than in the arbitrary manner so commonly seen—and it should allow for model expansion, if subsequently needed.

A parallel activity has been the development of models to describe the performance of individual organs and tissues of the body. In its simplest and commonly applied form, each tissue is regarded as a well-stirred system, yet experimental data sometimes point to the need for more realistic yet more complex models that take into account such factors as the various physical spaces within tissues, the existence of permeability barriers, organ heterogeneity, and active transport or metabolic processes.

PBPK MODELING FOR IMPROVEMENT OF THE DRUG DISCOVERY AND SELECTION PROCESS

There are many characteristics of the ideal drug candidate. One of these is that its pharmacokinetics should meet its intended use. Many potentially useful drug candidates, however, fail because the molecule has undesirable pharmacokinetic properties, such as poor bioavailability, thereby limiting oral administration, or poor metabolic stability, thereby severely limiting the possibility of once-daily administration. In the following paragraphs, a proposed strategy for model building in the very early phase of drug candidate selection is explored. This strategy is based on the separate simulation of the quantitative features of absorption, distribution, and elimination processes, followed by the integration of these 3 elements into a single PBPK model.

Early Candidate Selection

Ideally, it would be beneficial to be able to predict the pharmacokinetic behavior of a compound ab initio from its "molecular descriptors" (eg, lipophilicity, molecular size and shape, charge density distribution) alone, as then only compounds with desirable features would be synthesized and investigated further. Although not currently, if ever totally, realizable, nonetheless such in silico–generated descriptors may enable a reasonable initial prediction of the likely behavior in vivo of some processes, in particular those based on passive processes such as diffusion and simple partitioning (eg, into fat). However, the task of predicting the likely overall pharmacokinetic behavior in vivo is becoming more feasible by coupling in silico computations with pertinent in vitro data, such as plasma protein binding, microsomal or hepatocyte intrinsic clearance, and cell membrane permeability (eg, across Caco2 cells), which allow for the inclusion of active processes involved in metabolism and membrane transport. Using mechanistically based software (see Appendix 2) estimates can be made as to the expected rate and extent of absorption, the affinity of compound for individual tissues, and hepatic clearance, which when placed appropriately within a "generic whole body PBPK model" allows prediction of the temporal profile of a compound in both plasma and tissues. Verification and further refinement of this modeling approach can only be performed in animals, although often the ultimate objective is to predict likely profiles in humans.

As the required input parameters can be generated during early discovery, the application of generic PBPK models becomes feasible during the clinical candidate optimization and selection process. Such implementation would have several advantages: (1) it would aid in the candidate selection itself, as mentioned above, by improving the likelihood of selecting compounds with desirable PK properties; (2) it would result in a reduction in unnecessary animal testing, as it may well avoid the testing of compounds whose PK properties in humans are predicted to be inadequate for intended use; (3) being mechanistically based, it would contribute to a systematic and rational approach for identification of the key parameters of a compound that should be defined in early development, as it can be very expensive to first become aware of these much later in drug development; (4) the overall PK of potential drug candidates in animals (and humans, made possible through a combination of scaling of the physiological parameters and use of in vitro human data within the frame of the whole body PBPK construct) can be anticipated prior to any in vivo experiments, thereby helping to improve the design of such studies; and (5) it would improve the ability to more reliably extrapolate PK across species (see Figure 2), routes of administration, and dose levels. During the development process, additional data (eg, tissue kinetics during safety assessment) may be generated that can be used to improve the generic PBPK models by adding information and/or replacing in silico and in vitro input data. In this sense the in silico and in vitro–based PBPK modeling approach is complementary to the conventional whole body PBPK approach, which requires in vivo tissue kinetic data as input information.

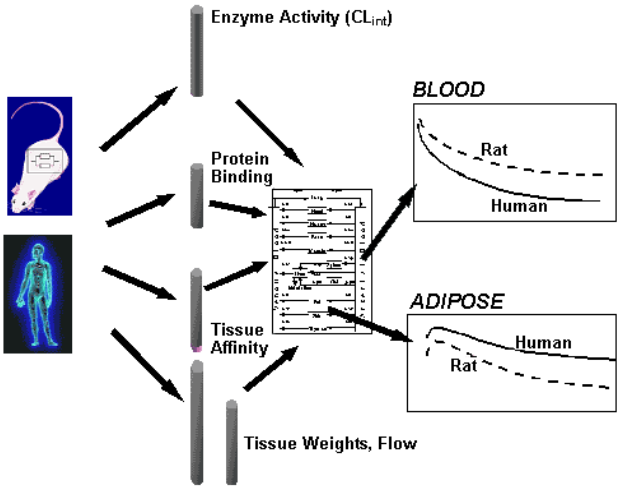

Figure 2. Schematic illustrating how differences in the magnitude of various parameters, such as intrinsic metabolic activity, plasma protein binding, tissue affinities, tissue volumes, and blood flow, propagated through a whole body physiologically based model, explain the differences in the concentration-time profiles in blood and tissues between rat (or any other animal) and human.

Preclinical Phase

There is a major push to predict the likely pharmacokinetic performances of drugs in humans from preclinical data, thereby helping to avoid evaluation in humans of compounds with poor pharmacokinetic performance, which can severely limit their practical use. Here, scaling forms an important element of the process. The allometric approach, which assumes that any differences across species are driven by body size alone, has long been the dominant method for interspecies scaling. However, due to the failure to account for differences in active processes, such as metabolism and transport, the use of this approach to predict the "first into human strategy" has come under significant criticism. At present, the decision is often taken based on toxicological and animal pharmacological considerations alone. From the available experience, it clearly appears that PBPK modeling offers a modern, science-founded approach to help rationalize the "first into human" decision-making process. By challenging the observed human data against predictions over many compounds, increasingly more accurate predictive PBPK models will be produced, although this approach is likely to be most successful within a series of structurally related compounds, as commonly arises in drug development. PBPK modeling also has the potential to explain certain aspects of species differences in nonclinical safety studies, such as accommodating for differences in tissue-specific transporters and binding constituents as well as in relative composition of body fat.

As clinical and commercial interest in a particular compound increases so does the range of studies surrounding it, including in vivo animal tissue distribution studies, as part of safety assessment. Here the opportunity arises to evaluate the ability of in silico and in vitro methods to predict tissue distribution, as well as to explore such facets as concentration dependence and permeability. Studies to date show that in many circumstances the distribution of a compound into a particular tissue is similar in animals and humans, which would suggest that the components of the tissue that are responsible for its distribution are common across the species, including their relative composition. Indeed, this is an almost universal assumption in the scaling of animal data to predict pharmacokinetics in humans, whether working with drug substances or environmental compounds. This assumption may not always hold, as often reflected by poor prediction of the volume of distribution of the compound in humans, even after correcting for differences in plasma protein binding across species. When the assumption fails, it is important that the reason for it be pursued, as the failure may be due to species differences in tissue composition of the primary binding constituents, which once characterized would allow cross-species prediction of tissue distribution for related compounds. Also, in vitro studies with human tissues, which have increasingly become available (liver being a well-known but by no means the only example), would allow greater study of the relevance of animal data to predict tissue distribution in humans, currently a relatively neglected area compared with in vitro studies of metabolism and absorption.

PBPK Modeling During Human Drug Development

Early human studies are normally conducted in healthy subjects to assess acute safety and, if applicable, to monitor biochemical and pharmacological responses. These studies also provide pharmacokinetic, metabolic, and biopharmaceutical data, all of which are essential to characterize the drug's profile in humans—ultimately in the target patient population. Physiological conditions, such as body weight and composition, hepatic and renal function, and cardiovascular function vary within and among patients and are often different from healthy subjects. Individuals also differ in their genetic profile, dietary habits, and in the case of patients, in the degree of

severity of disease and consumption of other drugs. PBPK modeling offers an improvement upon conventional approaches by providing a mechanistic framework for exploring, through computer simulation, the impact of these components and their variability on the likely variation in PK profiles in any part of the body within the target population. This, in turn, facilitates better design of future clinical studies, whether these are phase 2 or phase 3 clinical trials, and addresses the likely profiles in patients in a whole variety of clinical situations that are unlikely to be evaluated experimentally, but because of sufficient confidence in the model reasonable predictions can be made. In addition, PBPK provides a logical and quantitative link between various sets of data arising during early and late clinical studies, as well as linking animal and human data that may have relevance when attempting, for example, to relate animal exposure data to human exposure.

Currently, when estimating PK parameters from observed plasma data, the common practice is to drop the whole body PBPK approach on entry into human studies, even if applied in the preclinical phase, in favor of empirical approaches, such as the fit of a sum of exponentials or a simple compartmental model to the data. This practice may have some utility and pragmatism, given the higher dimensionality and complexity of whole body PBPK models. However, even under these circumstances, there would be benefit in having models as physiologic as possible, such as models for drug tissue distribution that incorporate physical aqueous spaces and plasma protein binding, and clearance models that incorporate blood flow and intrinsic cellular activity. There are, however, some situations in which PBPK may offer the only ethical approach to addressing concerns during drug development involving questions of tissue exposure and potential risks.

There have not been too many published applications of PBPK in regulatory decision making to date. However, one illustrative example is the evaluation of the safety risk potential of retinoic acid derivatives. In the early 1990s all-trans retinoic acid was being considered for marketing approval by the Food and Drug Administration (FDA) for the indication of photo-damaged skin (wrinkles). The FDA Center for Drug Evaluation and Research (CDER) director requested the sponsor to evaluate, using PBPK simulation, the potential fetal exposure to retinin-A applied topically in women of reproductive age. Aware that retinin-A, like its chemical neighbor 13-cis retinoic acid, is highly teratogenic (40 times more so than thalidomide) and that up to 10% of a topically applied dosage is absorbed systemically, FDA sought reassurance that fetal exposure and teratogenic effect potential would not result during clinical use. PBPK simulation was the only rational and ethical method of risk assessment available. The sponsor conducted a PBPK analysis that provided that assurance to the FDA during review and subsequent approval. This line of reasoning may be extended to similar situations involving potential safety issues associated with exposure at other tissue sites, such as the liver, kidney, or brain, as well as of the infant ingesting maternal milk from lactating women who might need to be prescribed medication. FDA encourages sponsors to adopt PBPK, when appropriate and depending on the questions, during drug development with the aim to facilitate and enhance the capability to make better predictions, improve understanding, and provide improved regulatory decision making.

PBPK AND PHARMACODYNAMICS

Classical PK/PD

At present linked pharmacokinetic/pharmacodynamic (PK/PD) modeling is progressing from an empirical, descriptive discipline into a more mechanistic science that can be applied at all stages of drug development. In the same way that pharmacokinetics has been moving toward a system-orientated approach in which drug-specific data are overlaid onto the physiologic/disease progression model, so too is pharmacodynamics. Increasingly, biomarkers are being identified and developed at a very early stage of drug development, often extending from animals to human studies as a readily determined and relatively rapid measure of drug effect on the body. Many of these biomarkers are endogenous compounds, such as hormones, in which the direct drug effect is to produce either a change in the rate synthesis or degradation of such compounds, with the time scale often a function of the turnover kinetics of the endogenous marker. Other biomarkers are functional measures such as a change in blood pressure or body temperature. In each case, an important element in the development of a mechanistically based PD model is the separation of drug-related properties (such as receptor affinity and intrinsic efficacy) from system-related properties (receptor density, stimulus-response relationship, and homeostatic control mechanisms), gained through dynamical systems analysis. Such mechanistic PK/PD models constitute a scientific basis for the following: (1) prediction of drug effects in vivo on the basis of results obtained from in vitro bio-assays, (2) allowing interspecies extrapolation of drug effects, and (3) for the understanding of intra- and interindividual variability in drug response. Most drugs act in cells and tissues, so that when estab-

lishing concentration-response relationships the use of plasma data, obtained from a peripheral vein, may hinder the ability to establish the relationship because of temporal differences, and even differences at equilibrium, between active site and plasma. Here PBPK, with its ability to predict the kinetics of drugs in tissues as well as plasma, has application.

Because of their ability to formally incorporate prior knowledge and sources of variability, Bayesian methods and the application of nonlinear mixed effects modeling are essential in the development of mechanism-based PK/PD models. Often information on different drugs and/or information on the same drug but obtained under different conditions needs to be simultaneously analyzed to derive the in vivo stimulus-response relationship and to obtain estimates of physiological rate constants of the dynamic system. Furthermore, the incorporation of information from different sources (ie, in vitro bio-assays) may be required.

Environmental Risk Assessment Using PBPK

There is a close relationship between environmental risk assessment and risk assessment of therapeutic agents. The main differences are that in environmental risk assessment, chemicals not intended for human therapeutic or nutritional consumption must be studied but cannot be administered to human volunteers, chemical toxicity is the main objective of observation, and the principal aim is to inform risk assessment and reduction procedures. On occasion, human data are available from accidental exposure to such chemicals.

The process of assessing the health risks associated with human exposure to toxic environmental chemicals inevitably relies on several assumptions, estimates, and rationalizations. Some of the greatest challenges result from the necessity to extrapolate from the conditions in the studies providing evidence of the toxicity of the chemical to the anticipated conditions of exposure in the environment or workplace. For risk assessments based on animal data, the most obvious extrapolation that must be performed is from the tested animal species to humans. However, others are also generally required: from high dose to low dose, from one exposure route to another, and from one exposure time frame to another. PBPK modeling provides a powerful method for increasing the reliability of these extrapolations and is one that is being increasingly accepted by environmental protection agencies.

AVAILABILITY OF SOFTWARE

Users

PBPK software development is very expensive and the user group is relatively small, at least at the moment. It appears that the community of PBPK technology users is neatly split between "experts" (ie, those who actually have done PBPK modeling using any software tool that they had at their disposal) and "novices" (ie, those about to use PBPK models for the first time). This view is probably simplistic and does not represent the reality exactly. It is nevertheless useful for a discussion of present needs in software. In general, "experts" have little need for, and do not see the relevance of customer-built, specific, or user-friendly software, as they are usually experts also in general modeling methodology (eg, ordinary differential equations, probability theory, etc). In contrast, novices need user-friendly tools that encourage them to learn PBPK modeling and to appreciate its limitations. Given this split, there is no single preferred software available that meets all needs.

Software for Whole Body PBPK Modeling

Software for whole body PBPK, as with other PK tools, should be able to perform both simulation and parameter optimization. It appears that there is an inverse relationship for existing software between user-friendliness and flexibility. Appendix 2 provides a listing of available software for PBPK modeling, including in silico prediction. It ranges from low-level programming languages, generic tools developed primarily for engineering purposes, to tools for biological or PK/PD modeling. The problem of in silico prediction has been briefly mentioned in the Early Candidate Selection section. Absorption, distribution, and metabolism may be simulated using a variety of software. However, currently there does not seem to be specific software for the simulation of excretion, and the current practice at least for renal excretion is to scale renal clearance across mammalian species using allometric relationships, which seems to work adequately for this particular process.

Standardization

The presently available software is very diverse in both quality and scope of application. A future goal could be standardization; this would ensure that whoever uses PBPK technology does so in a way that is reasonably uniform with that done by others in the field. This is certainly not the case today, raising serious problems of model verification. That said, it is doubtful that this goal of standardization will ever be truly reached in view of

the diverse objectives of PBPK modeling, but all steps toward this goal are to be encouraged if PBPK modeling is to be more widely applied. Further impetus for standardization may come from regulatory agencies, which encourage and sometimes require fully transparent characterization and validation of software that is used for official submission of data to support marketing applications.

PHYSIOLOGICAL AND ANATOMIC DATABASES

Various sources of physiological and anatomical databases exist. Some of these sources are listed in Appendix 3. As PBPK develops, the need for creating additional databases will exist, particularly in the human arena, such as those listing changes in blood flow and the composition of individual tissues and organs varying with age, or for particular diseases, such as diabetes. In some cases, the needed information is currently lacking or poorly assembled, and additional work is needed to accumulate and appropriately assemble the information.

There are, however, numerous concerns with existing databases: assumptions and conditions are often not specified; there is inconsistent or even unknown quality control of the data; information on variability of parameters is frequently lacking; the techniques and methodologies used to derive normative data can vary, with unknown impact of the resultant information; it is often necessary to go back through multiple references to get to the original data; and/or information in both healthy and disease states is not available. Also, the same amount and quality of such data are often not available across all animal species likely to be used in drug discovery and development. As a consequence, there is a strong need to build a validated physiologic database. Model libraries and databases should also be integrated with the "ideal" software to provide adequate input and data in order to maximize the applicability of PBPK modeling. Here again, as with software, the task of producing these databases should not be underestimated, and in the meanwhile any user of PBPK modeling should be or should become familiar with the quality of the physiological and anatomical data that they intend to use.

PRACTICAL ISSUES

Parsimony and Model Validation

Compartmental analysis has its tradition of parsimony derived from the fact that model selection is "data-driven." As an example, from a data set informing a mono-exponential curve it is not possible to derive more than 2 parameters. The situation is different for PBPK models but the need to respect some rules of parsimony remains. However, model parsimony is certainly less of an issue with PBPK than with traditional compartmental modeling. In the context of PBPK, parsimony is always a matter of degree and is not absolutely necessarily something to strive for. One may state that the "best" model is the one that answers critical questions with a maximum level of reliability. As a consequence, even if parsimony is less critical with PBPK than with other types of models, it remains an issue to be considered.

PBPK models are complex ones in which not all the unknown parameters can be estimated using formal identification procedures. Among different strategies, the following approaches can be considered to gain some confidence in the reliability of the model: (1) increase model testability by decomposition into its subsystems, (2) examine model prediction for a wide range of physiological and abnormal conditions, and (3) study the effect of parameter uncertainty on model plausibility (eg, through various forms of sensitivity analysis).

Variability and Uncertainty

It is important to distinguish at least conceptually between methodological uncertainty and inherent biological variability. In practice, the distinction is often less clear. The important step is to try to minimize uncertainty, thereby revealing the underlying variability in parameters that exists within and between individuals. Sources of methodological uncertainty include assay error; poor handling of samples, especially when dealing with in vitro systems; poorly defined scaling factors; a too small or nonrepresentative sample; and misspecification of components of the PBPK model, and of the global model itself. Several of these factors, such as assays and in vitro methods can be examined critically through independent investigation; for others, such as model structure, it may be investigated systematically against the data through sensitivity analysis. Distinguishing between methodological uncertainty and biological variability is relevant when analyzing for the impact of changes in input parameters on prediction of underlying events within the populations, where variability is the inherent issue. Methodological uncertainty should be included when considering the range of observations likely to be encountered in practice.

Model Verification and Documentation

As in any form of modeling, verification is an important issue in PBPK. Verification should be considered as a multidimensional approach that reflects current theories and experimental data relating to the particular system of interest, together with model purpose, formulation, and identification. A similar problem arises for model documentation, in particular for publication in the scientific literature. Because of page-length limitations in most journals, model documentation is often reduced to such an extent that it cannot be fully analyzed by the reviewers and used for replication studies by other scientists. Solutions to this problem should be found, for example, by making this information available to the reviewer and later for the interested readers through a Web site.

Quality of Input Data

The quality of data derived from databases has been briefly mentioned in the Physiological and Anatomic Databases section. The same concerns may be raised for the molecular properties used for in silico prediction or in vitro data used for estimation of parameters characterizing absorption, distribution, and metabolism. Of particular concern is that in vitro data, although usually are quite reliable from a qualitative point of view, are much less reliable from a quantitative viewpoint. Another limiting factor is the variability in some assay system components. A good example is illustrated by the use of human hepatocytes: their availability seems to be inversely correlated with the hepatocyte "quality" (including the amount of information available on the donor). On the other hand, animal hepatocytes are not always optimal, in particular when a given species does not express enzymes important for metabolism in human beings.

EDUCATION AND TRAINING

Issues related to education and training were discussed in some detail during the workshop. These have a particular bearing on the prognosis for the wider application of PBPK modeling to improve the discovery and development process of new pharmaceutical agents. One major limitation is that there are few university centers seriously engaged in PBPK research, and consequently few researchers available to apply this approach. Some researchers are engaged in the pharmaceutical arena, but more are to be found researching aspects of environmental exposure and risk assessment. Although these two communities have many interests in common, they currently tend to be distinct. There would be much benefit in them working more closely together, as well as collaborating with governmental agencies and industry, where much of the drug-related data are, or can be, generated. While not solving the manpower problem per se, this collaboration would progress the research and general awareness more rapidly. As to manpower, in the short term the solution is through the provision of courses and workshop for staff either already in industry or governmental regulatory agencies, or thinking of entering the field.

The availability of user-friendly software would also greatly facilitate the training of new PBPK "modelers." Such software could be used to lead the novices through model building via examples and help them try ideas early in the development and modeling process through a "simple" interface. Tasks like model selection (eg, how many compartments in a tissue model?) would be greatly facilitated by appropriate software.

The novices and more experienced users of PBPK modeling are a diverse community ranging from mathematicians to engineers and biologists. When training prospective users, the theory (modeling methodology and biology) and the practice (practical software usage) should be closely integrated. However, some users may find it very difficult to grasp both. A combination of local (eg, within company) mentoring and outside training (eg, workshops) would be useful. Both short- and long-term training programs, as well as continuing interactions through user groups (such as the PharmPK Discussion Group (www.boomer.org/pk) and the NONMEM User Network (nmusers@globomax.com) may constitute a proper and gradual introduction to the required modeling competencies.

Finally, despite the above-mentioned limitations, there appears to be growing demand for individuals with training in PBPK. This is especially true in the areas of drug discovery, candidate selection, and early clinical development. It is anticipated that this demand will increase over time, as the benefits of its successful application become more widely recognized.

MANAGEMENT AND CULTURAL ISSUES

There are several management and cultural obstacles to the implementation of PBPK modeling with the pharmaceutical arena. In many ways, one obstacle impacts on the other. A major obstacle is that management is often both uninformed and unconvinced that PBPK modeling adds significant value over traditional approaches or, indeed, is not convinced about the value of modeling in general. This is not always the case, and there are companies attempting to implement PBPK modeling by creating cross-functional teams that serve

as a fertile environment for mentoring young scientists. A team approach is necessary because successful application of PBPK requires broad knowledge in a wide range of scientific disciplines, which is unusual to find in any one person. These disciplines include pharmacokinetics, pharmacodynamics, mathematics, statistics, computer science, physiology, pharmacology, pathology, biology, and toxicology. Some companies have even gone so far as to create Centers of Excellence that bring together the needed communities of practice and provide broad representation of these ideas to improve acceptance. An important first step for these cross-functional teams is the need to prospectively define and plan for those situations within their company in which PBPK would be particularly helpful, examples of which have been identified in this report. It is also important to realize that one cannot think of applying whole body PBPK to clinical drug development, such as in the simulation of clinical scenarios, unless it has been implemented in the drug discovery, preclinical phase, as much of the relevant information needed for simulation and modeling, such as tissue distribution, is gained in these early stages. Hence, the team must have staff from both discovery and development.

Another obstacle is the "time to market" pressure. Scientists who are assigned to discovery or development teams are given large project loads and many tasks have to be performed in a very short period of time. This provides little opportunity for the development of new modeling techniques and reflection on their implications. The lack of time to "go back" and fill in the details means that if prospective opportunities are not created for the application of PBPK, by the formation, for example, of a modeling group, and the time is not invested in planning for its implementation and application with drug development, it will be difficult for these modeling approaches to rise to the forefront.

REGULATORY ENVIRONMENT

The drug development and regulatory environment are both likely to have a significant impact on the pace and scale of implementation of PBPK modeling within industry. In the environmental protection area, at least within the United States, PBPK is used as part of the decision-making process in many situations, and it is being increasingly encouraged by environmental protection agencies elsewhere in the world. The situation within drug regulatory agencies is much different. In some respects, the situation of PBPK now closely resembles the situation found some years ago with population PK/PD. Despite the initial reluctance of companies to undertake such population studies, this component of drug development, particularly in clinical trials, is now much more common. Regulators insist that they are very interested in tissue exposure, for example, particularly as it bears on certain aspects of safety, but do not mandate specific approaches to help address the issue. It is clear that PBPK could be a useful approach in addressing some of these, and other, issues, as mentioned in the PBPK Modeling During Human Drug Development section. In addition, regulatory agencies have a wealth of information on such aspects as how drug metabolic activity varies with age, disease, and ethnicity that could well be incorporated into PBPK models to predict the likely variation in PK parameters within the population. However, this information is also widely available in the literature for those in drug development who need such information for their PBPK studies.

CONCLUSION

The salient points to emerge from this workshop are as follows:

- Whole body physiologically based modeling provides a mechanistic, holistic approach to both understanding the pharmacokinetic behavior of compounds and predicting what is likely to happen in plasma and tissues over a wide range of conditions.
- A PBPK model comprises three components: a body of independent physiological, anatomical, and biochemical data— *the system*; drug-specific data overlaid on to the *system*; and the model structure, this being the tissues and organs included in the model and their arrangement. As our knowledge of the system and how drugs interact with it increases, so will the ability to predict the likely pharmacokinetic behavior of drugs from relatively limited drug data. To provide meaningful predictions, it is important to incorporate biological variability and methodological uncertainty in parameter values throughout the modeling process.
- Drug specific data from different sources, in silico, in vitro, and in vivo, can readily be incorporated into PBPK models. However, it is critical to verify at every opportunity the utility of the input data against events of interest in vivo.
- The PBPK model approach is flexible in the sense that it has the potential to be continuously updated in the light of new information, whether physiologic, disease, or drug related, including up- and down-regulation of critical components.

- The power and utility of PBPK modeling would be further increased when linked with mechanistically based pharmacodynamic models.
- PBPK models aid in the more accurate and informative prediction of human pharmacokinetics from in vitro and preclinical data, and in the pharmacokinetics of drugs in various clinical situations. They also allow the possibility to examine plausible and likely outcomes in situations where there are severe ethical constraints to experimentation.
- PBPK modeling in clinical drug development can be optimally applied when implemented at the preclinical stage. It therefore requires cross-functional teamwork for its practical application.
- The regulatory receptiveness and encouragement for the use of PBPK modeling and simulation to address various clinical questions will influence the pace and extent of its adoption and application during drug development.
- Obstacles to the wider use of PBPK modeling are manifold, including uninformed management attitudes, suboptimal organizational structures, lack of user-friendly modeling software, lack of appropriate and easily accessible relevant physiological and related databases, and, of importance, lack of adequately trained researchers in PBPK modeling. All, however, are soluble if there is willingness in the pharmaceutical, regulatory, and academic communities to address these obstacles.

Finally, PBPK, especially when linked with PD, has great potential to assist in the optimum design, selection, and development of drugs. However, in order to improve its acceptance within the pharmaceutical industry and by regulatory agencies, it will be important to publicize attempts at PBPK(PD) modeling with respect to both successes and failures and to highlight the role that these analyses have played in decision making. This would improve and expedite effective development of this mechanistically integrated approach. It would also help to create a continuous feedback loop between preclinical and clinical teams and help to further promote scientifically and rationally guided drug discovery and development.

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APPENDIX

Appendix 1: Selected References

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Appendix 2: Software with Web Sites

General-Purpose High-Level Scientific Computing Software: The following packages are high-level programming or matrix languages that provide very general tools for scientific computing. Their use for PBPK modeling implies that investigators may need capabilities that more user-friendly software does not provide.

Berkeley Madonna, University of California at Berkeley: http://www.berkeleymadonna.com/

MATLAB-Simulink, The MathWorks, Inc: http://www.mathworks.com/

MLAB, Civilized Software, Inc: http://www.civilized.com/

GNU Octave, University of Wisconsin: http://www.octave.org/

Biomathematical Modeling Software: The tools in the following list have been designed explicitly for mathematical modeling of biological systems. Some have a user-friendly (graphical) interface, and their manuals are usually designed to appeal to the biomedical investigator. The degree to which they can be used for PBPK modeling is dictated by the limitations imposed by the graphical interface, speed of computation, and flexibility of the modeling language. Some of these tools also provide mixed-effects (population) capabilities, with which, at least in principle, sparse data sets can be analyzed.

ADAPT II, Biomedical Simulations Resource, USC: http://bmsr.usc.edu/

ModelMaker, ModelKinetix: http://www.modelkinetix.com/

NONMEM, University of California at San Francisco and Globomax Service Group: http://www.globomaxservice.com/

Stella, High Performance Systems Inc: http://www.hps-inc.com/

WinNonlin, Pharsight Corp: http://www.pharsight.com

SAAM II, SAAM Institute Inc: http://www.saam.com

Toxicokinetic Software: The following tools were explicitly designed for PBPK and PBTK modeling. They are extremely flexible and are direct descendants of modeling languages developed in the aerospace industry for M&S of complex systems.

ACSL Toxicology Toolkit, AEgis Technologies Group Inc: http://www.aegistg.com/

SimuSolv, Dow Chemical [not maintained or subject to further development]

Physiologically Based Custom-Designed Software: The following list contains proprietary software systems that are custom designed for specific biomedical systems or applications. As such, they provide a very high level of biological detail for the specific system they were

developed for, but for that very reason they are not easily customized by the investigator.

GastroPlus, Simulations Plus Inc: http://www.simulations-plus.com

Pathway Prism, Physiome Sciences Inc: http://www.physiome.com

Physiolab, Entelos Inc: http://www.entelos.com/

Appendix 3: Sources of Physiological Information

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