Physiologically Based Pharmacokinetics as a Component of Model-Informed Drug Development: Where We Were, Where We Are, and Where We Are Heading

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Model-informed drug development (MIDD) or its alternative (more European) acronym MID3 (Model-informed Drug Discovery and Development) has now become synonymous with the integration of all relevant and available information in helping with decision making during the process of drug discovery and development. This approach does not claim that decision making in the absence of MIDD is made arbitrarily, but it is suggesting that nonquantitative integration of information by individuals (what is coined as in-cerebro modeling) is reaching its capacity with the overflow of information leading to some pieces being missed out, or their influence underestimated. Apart from questions on the rigor of connecting various pieces and optimality, another downside of the in-cerebro approach is the inability to trace and document the elements that made up the decision thus reducing reproducibility. It is no surprise, therefore, that in 2016 the MID3 Workgroup of the European Federation of Pharmaceutical Industries and Associations provided a strong argument and advocacy for greater applications of MIDD, with a long list of successful examples on various applications.1

More recent perspectives from several regulatory scientists have indicated that the regulatory path for MIDD is not only “open” but is “welcomed” provided that the efforts follow the best practices.2,3 So the MIDD approach and in-silico studies are not just for internal decision making within pharmaceutical companies but are now an accepted and much encouraged element of the regulatory approval process too. In-silico studies are not an alternative to the clinical studies that ought to be carried out, but they can potentially replace studies where the outcome is a priori known with high certainty under integration of all available data (whether the outcome is negative or positive). Of course, they can fill the gap created by clinical studies that are unlikely to be conducted for many logistical reasons by providing more rational support for making clinical decisions than the alternative less reliable in-cerebro integration of information and associated decisions. This is something that often happens for off-label use in subgroups of patients such as neonates, infants, pregnant women, patients with renal or liver impairment, and so on.4

Unfortunately, despite the formal recognition of MIDD in Section 3 of the Prescription Drug User Fee Act VI by the US Food and Drug Administration (FDA),5 there are many pharmaceutical companies where MIDD is not common practice or is not even known as a path for drug development. Smaller companies in particular might be at a disadvantage when there is no internal bandwidth to support all the quantitative integration of modeling efforts needed, whether these are related to selection of dose and dosage regimen, supporting evidence for efficacy, design of efficient clinical trials, and optimal sample size among other things. Nonetheless, as MIDD is moving from a “luxurious, nice-to-have” tool to an “essential must-have” kit in drug development, this perspective briefly looks back at the role that physiologically based pharmacokinetics (PBPK) has played over the past decade as a piece of

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MIDD and outlines various uncharted territories that PBPK is entering into while pushing the boundaries of MIDD.

Revisiting PBPK and Its Journey

In reality, PBPK is a subsector within the broader discipline of mechanistic biological systems modeling. As long ago as 500 BC, the Pythagoreans believed that all natural phenomena should be reducible and explained by a relationship between numbers. Increasing quantitative understanding of biological processes, mechanisms, and systems and the impact or causation of disease and pharmacological intervention is facilitating the development of increasingly sophisticated and granular biological systems models, describing biology in terms of mathematics. PBPK models of increasing sophistication that incorporate mechanistic understanding of not only drug-metabolizing enzymes but cellular efflux and influx transporters, fetal drug disposition, and the impact of the interplay between drug and formulation excipients upon drug absorption are being developed and deployed with great success. Whereas historically prevalent pharmacostatistical models, built upon prior experimental data and their associated statistical variability, have demonstrable utility of interpolated prediction within the boundaries of a current practical experience, the excitement surrounding mechanistic biological systems modeling (of which PBPK modeling and simulation is perhaps the most advanced example in terms of drug development and regulatory science) is in its potential to predict outcomes outside of currently explored experimental boundaries. The ability to predict outcomes that are experimentally intractable from either an ethical, practical, or financial perspective is a tantalizing prospect. Moreover, the opportunity to explore what-if scenarios prior to unnecessary and costly iterative experimentation is of immense value and arguably the ethical way forward if human or animal investigation is necessary.

Looking Back

The majority of applications of PBPK in the past century were limited to environmental science and toxicology.6 Hence, many scientists who have not been close to the new applications of PBPK have a different perception of what PBPK stands for than those who have entered this field over the past 2 decades. Throughout the 20th century, PBPK was synonymous with tissue distribution of xenobiotics in animals and humans. The latter modality of use is continuing and involves building sets of differential equations manually in various modeling platforms, where the focus is often the “model” and the specific “compound.” This is no longer the center of attention or common practice, at least within the pharmaceutical arena, for several reasons (see the next section). The tremendous success gained in establishing various in vitro systems and extrapolating the output from such systems via quantitative/mechanistic models to in vivo consequences has been at the heart of the shift from old PBPK to the new PBPK combined with in vitro to in vivo extrapolation (IVIVE). However, the expansion in the usage has meant that the requirement for consistency and quality could not be maintained when the models were built as an individual compilation of sets of equations. The shift required a consensus to be reached on the models that could be reused by many investigators. Although currently PBPK is considered under systems biology modeling, this was not the case until IVIVE was incorporated into PBPK.7

Current Status

The focus of contemporary PBPK (or, as we defined above, PBPK-IVIVE linked models) is to create a framework that provides the most rational answers to multiple questions related to the fate of the drug in various populations and under different conditions rather than addressing just a single issue. Therefore, integrating the known information on systems attributes (in various conditions), which are independent of any drug, takes a higher priority. It is the interaction of the compound characteristics (often measured in vitro or estimated via quantitative structure-activity relationships) that determines which components of the system will be playing a role and which ones will have no impact. This approach has resolved much confusion regarding different pharmacokinetic behaviors of closely related drugs, for instance, in the case of cytochrome P450 3A compounds and the change of clearance from neonates to adulthood.8 The evolving nature of new PBPK has meant that the acceptance of outcome and interpretation of findings do not have equal standing and value in various areas of application. Some areas are relatively well established, while others remain the subject of debate and much-needed discussions among scholars (see the next section). In 2012, editorial comments, in a special issue of *Biopharmaceutics and Drug Disposition* that was dedicated to PBPK, included the statement “PBPK is here to stay!”9 with a view to warn those who were dismissing the advances, and prepare them for the logistical future needs. Issuance of regulatory guidance notes on PBPK10,11 in 2018 was a clear indication that the predictions of the influence of PBPK were correct and as Rowland et al12 stated, PBPK had moved from an academic curiosity to an industrial necessity and a level of regulatory acceptance that was associated with issuing guidance notes for industry. The wide areas of application are captured from a regulatory angle and occasionally published by
the Office of Clinical Pharmacology at the FDA. Although the majority of reviewed applications in investigational new drug/new drug application submissions by the FDA’s Office of Clinical Pharmacology involves support enzyme-transporter-mediated drug-drug interactions, there are other applications in areas such as the effect of organ impairment, food, age (neonate and pediatric), ethnicity/genetics, and a combination of these factors as indicated by Table 1 in Grimstein et al. It is noteworthy that the current status of PBPK applications outside the commonly considered “green” zone of metabolic drug-drug interactions are considered on a case-by-case basis by regulators. However, whether they are in the “amber” zone where there is some prior experience or in “red” zone where there is no prior experience, submission of all applications are encouraged to enable broadening the experience and databases for various usage of PBPK.

Ongoing Debates

PBPK and mechanistic biological systems modeling as a whole has its critics and skeptics. Much of the criticism has focused on what is touted as the intrinsic strength of the approach: the ever-expanding “granularity” or mechanistic detail of such models. Overparameterization of models and issues relating to model identifiability have often been a central theme of criticisms from the pharmacostatistical community or that such models, by their very nature, are built on beliefs or prejudiced opinions that may bring constraint and prevent the data speaking for themselves. Within such criticisms are truths and without doubt more statistical rigor must be brought into the mechanistic modeling arena. But while parsimony may be still considered as mathematical model building best practice, a naive reductionist approach, without understanding the underlying biological processes and mechanisms, could result in “throwing the baby out with the bathwater” as the decision as to what parameters/processes are truly additive to the model can be based only on experiences to date and cannot speak to the potential importance of the parameter/process/pathway in the future and thus limit the ability to extrapolate. Perhaps the most valid criticism of mechanistic models relates to the inability to measure/test/validate some of the granules within such models, but with advances in imaging technologies, liquid biopsy and other noninvasive methods of assessing physiological and biochemical processes, the current walls of these limitations will in turn crumble.

Near-Term Future

The principles of building a common toolkit, particularly with a precompetitive collaboration between pharmaceutical companies, is now well accepted and recognized (albeit not unanimously). The issue of quality for input parameters (whether drug or system specific) is going to engage the researchers in the PBPK area in the near future. However, it seems based on large-scale studies with predefined measures and blinded studies that the variations associated with the “operators” of these systems are much less appreciated. These variations are usually associated with the selection of the parameter and experimental settings, which is related to the availability of multiple options for any given drug. Although common platforms have reduced the arbitrary/individual decisions as a cause of variation and rise in PBPK outputs, considering the wide range of inputs, decisions made by a group of experts rather than a single individual is essential when trying to go with the most prudent input parameters. As detailed, there is a lot to be optimized beyond the mechanics of the tools and the values themselves, which are related to the policies and infrastructure for operationalizing the routine use of PBPK as part of MIDD.

Long-Term Future

Current PBPK models are built based on virtual populations and attributes defining any subgroups using a combination of systems information when they are known to be different (eg, abundance of enzymes and transporters, frequency of certain genotypes, demographics) and traditional top-down modeling of available clinical data through reverse translation. Until recently, there was no feasible way to obtain individual information on abundance of proteins relevant to the fate of the drug (enzymes/transporters) in various tissues. The invention of liquid biopsy and the possibility of linking the measured values in plasma to actual protein levels in the tissues has changed the paradigm and has brought us one step closer to using PBPK as the basis for creating “virtual twins” and consequently to individual dosing. A number of leading pharmaceutical companies have already started to wrestle with the idea of using such methodologies for personalized dosing. Of course, this may increase the cost of the treatment; however, this can be offset against the potential reduced side effects or lack of efficacy. As the reimbursement models for the cost of medicines moves toward outcome-based approaches, the use of personalized dosing, no matter how far-fetched they may appear at this moment, will become more attractive options.

Epilogue

PBPK has become an integral part of the MIDD armory. While some corners of industry may not see it as an indispensable tool, many pharmaceutical companies have not only adopted the approach, but they have
also been finding new applications all the time. The usage has not been unanimous, as optimal application requires investment on many aspects beyond the PBPK tool itself. Front-loading of many in vitro experiments, creating a culture of closer collaborations between field experts and getting consensus on selection of model components and drug-independent model parameters are among the areas that require investment. Nonetheless, nothing will influence the direction of the PBPK development within MIDD more than the questions that clinical pharmacologists pose as pressing issues. This is particularly true when it is not feasible to address such questions via clinical studies or they require a bottomless pit of money such that they put the economy of safe and effective drug development for each and every patient in jeopardy. PBPK is entering into uncharted territories (Figure 1); however, past experiences have shown that by working together we may navigate through any unforeseen hurdles and land in places that we may not even have dreamed of in the past.19

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### Conflicts of Interest

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