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PBPK's Pivotal Role in Modern Drug Development: Busting Common Myths and Misconceptions

Amin Rostami-Hodjegan, Masoud Jamei, & Thomas Polasek

TOP TEN PBPK MYTH BUSTERS

1. Documented use of PBPK for drug approvals clearly demonstrates its regulatory necessity
2. PBPK is a simulation workhouse at all stages of development
3. The Simcyp Simulator delivers "open science in a glass box"
4. A rapid rise of prevailing peer-reviewed evidence demonstrates the benefits of PBPK
5. Regulatory agency guidance facilitates growth in PBPK submissions
6. Sharing PBPK data with regulatory agencies early increases the chance for waivers
7. Dynamic models answer current and future questions
8. PBPK applications are expanding beyond the prediction of DDIs, setting the stage for widespread acceptance
9. PBPK can be used for both small molecule and biologic drug development
10. PBPK is transitioning from R&D to clinical practice

PBPK's Pivotal Role in Modern Drug Development: Busting Common Myths and Misconceptions

Physiologically-based pharmacokinetic modeling and simulation (PBPK M&S) is a mechanistic modeling approach, actively encouraged by regulators, increasingly leveraged by biopharmaceutical companies, and used by key academics to optimize drug discovery and development by integrating pre-existing knowledge to synthesize new insights. Hence, PBPK is used to inform key research and development (R&D) decisions relating to clinical trial design, first-in-human (FIH) dosing, formulation design, treating special populations, and predictions of the likelihood of drug-drug interactions (DDIs).[1] Although early applications of PBPK were limited to risk assessment of environmental chemicals and animal/human toxicology, technological advances have transformed PBPK into a systems biology "superhero" in the modern drug development toolbox.

PBPK—A Systems Biology Approach to Drug Development

PBPK falls under the systems biology umbrella that applies a nonlinear, integrative, quantitative, and holistic approach using biology, computational modeling, engineering, bioinformatics, and other sciences to understand the complexity of biological systems. The development and evolution of "omics" technologies, eg, genomics, proteomics, transcriptomics, metabolomics, and others—the underlying building blocks of systems biology research—has led to better understanding of how diseases result from perturbations of biological networks. These learnings have advanced the field of systems biology, and notably with PBPK.

For example, PBPK modeling can predict an initial dose for new drugs in patients not studied in the pivotal trials by using characteristics of the drug from *in vitro* studies and the knowledge of patient attributes that defines the fate of the drug and hence the required concentrations at the site of effect. Using a mechanistic biological *in silico* approach, PBPK models can be built for virtual patient populations and used to account for the concentration of drugs in most tissues within the body.

Recent years have shown a surge of PBPK M&S within the pharmaceutical industry, and there has been strong support by global regulatory agencies for drug approvals. The positive impact that PBPK has brought to drug development has been clearly proven, saving considerable time and money while also providing the ability to ask and answer many "what if" questions.[2,3] However, change can bring its share of doubt and skepticism, and for years the value of PBPK has not been fully understood. This white paper addresses common PBPK myths and misconceptions and demonstrates how this approach is an industrial and regulatory necessity in modern drug development.

Myth: PBPK is an academic exercise versus a regulatory necessity

PBPK has become a regulatory driver not only for sponsors submitting new drug applications, but by regulatory agencies looking to optimize the drug development and regulatory review processes. In fact, the FDA has increasingly been encouraging sponsors to use mechanistic modeling to better understand the complexities of drug disposition and potential issues within broader populations. Most important, the Simycp® Simulator has been used to inform nearly 50 novel drug applications, including more than 200 label claims made without the need for clinical trials (Figure 1).

Figure 1: The use of Simcyp Simulator to inform label claims on novel drugs

- **Pfizer**: Revatio (sildenafil) — Pulmonary Arterial Hypertension
- **Novartis**: Odomzo (sonidegib) — Basal Cell Carcinoma
- **Genzyme**: Cerdelga (eliglustat) — Gaucher Disease
- **Novartis**: Farydak (panobinostat) — Multiple Myeloma
- **Eli Lilly**: Verzenio (abemaciclib) — Metastatic Breast Cancer
- **Novartis**: Kisqali (ribociclib succinate) — Metastatic Breast Cancer
- **Novartis**: Rydapt (midostaurin) — Acute Myeloid Leukemia
- **J&J**: Xarelto (rivaroxaban) — Deep Vein Thrombosis and Pulmonary Embolism
- **Janssen**: Olysio (simeprevir) — Hepatitis C
- **Sanofi**: Jevtana (cabazitaxel) — Prostate Cancer
- **Eisai**: Lenvima (lenvatinib) — Thyroid cancer
- **Intercept**: Ocaliva (obeticholic acid) — Primary Biliary Cholangitis
- **PTC Therapeutics**: Emflaza (deflazacort) — Duchenne Muscular Dystrophy
- **Ariad**: Alunbrig (brigatinib) — Metastatic Non-small Cell Lung Cancer
- **Tibotec**: Edurant (rilpivirine) — HIV infection
- **Actelion**: Opsumit (macitentan) — Pulmonary Arterial Hypertension
- **Novartis**: Zykadia (ceritinib) — Metastatic Non-small Cell Lung Cancer
- **Genentech**: Alecensa (alectinib) — Non-small Cell Lung Cancer
- **Actelion**: Uptravi (selexipeg) — Pulmonary Arterial Hypertension
- **Shionogi**: Symproic (naldemedine) — Opioid Induced Constipation
- **Janssen**: Erleada (apalutamide) — Non-metastatic Prostate Cancer
- **Ariad**: Iclusig (ponatinib) — Chronic Myeloid Leukemia
- **Pharmacyclics**: Imbruvica (ibrutinib) — Mantle Cell Lymphoma and Chronic Lymphocytic Leukemia
- **Pfizer**: Bosulif (bosutinib) — Chronic Myelogenous Leukemia
- **AstraZeneca**: Tagrisso (osimertinib) — Metastatic NSCLC
- **Janssen**: Invokana (canagliflozin) — Type 2 Diabetes
- **Spectrum**: Beleodaq (belinostat) — Peripheral T-cell Lymphoma
- **Helsinn**: Akynzeo (netupitant/palonosetron) — Chemotherapy-induced Nausea and Vomiting
- **GW Pharma**: Epidiolex (cannabidiol) — Lennox-Gastaut Syndrome or Dravet Syndrome
- **AstraZeneca**: Movantik (naloxegol) — Opioid Induced Constipation
- **Alkermes**: Aristada (aripiprazole lauroxil) — Schizophrenia
- **Amgen**: Blincyto (blinatumomab) — Acute Lymphoblastic Leukemia
- **Merck**: Prevymis (letermovir) — Cytomegalovirus
- **UCB**: Briviact (brivaracetam) — Epilepsy
- **AkaRx**: Doptelet (avatrombopag) — Thrombocytopenia
- **Eli Lilly**: Olumiant (baricitinib) — Rheumatoid Arthritis
- **Genentech**: Cotellic (cobimetinib) — Metastatic Melanoma
- **AstraZeneca**: Lynparza (olaparib) — Advanced Ovarian Cancer
- **AstraZeneca**: Calquence (acalabrutinib) — Mantle Cell Lymphoma
- **Merck**: Steglujan (ertugliflozin and sitagliptin) — Type 2 Diabetes
- **Vertex**: Symdeko (tezacaftor/ivacaftor and ivacaftor) — Cystic Fibrosis
- **Agios**: Tibsovo (ivosidenib) — Relapsed or Refractory Acute Myeloid Leukemia
- **Verastem**: Copiktra (duvelisib) — Lymphoma
- **Shire**: Motegrity (prucalopride) — Constipation
- **AbbVie**: Orilissa (elagolix) — Endometriosis
- **Pfizer**: Lorbrena (lorlatinib) — ALK-positive Non-small Cell Lung Cancer
- **Merck**: Pifeltro (doravirine) — HIV
- **Loxo Oncology**: Vitrakvi (larotrectinib) — Solid Tumors Based on Tumor Genetics

Dr. Scott Gottlieb, Commissioner of the FDA, has been an outspoken advocate for the use of innovation to advance the delivery of safer, more effective medicines for patients. In describing the steps needed to implement the 21st Century Cures Act, Dr. Gottlieb states, *"Modeling and simulation play a critical role in organizing diverse data sets and exploring alternate study designs. This enables safe and effective new therapeutics to advance more efficiently through the different stages of clinical trials. FDA's efforts in modeling and simulation are enabled through multiple collaborations with external parties that provide additional expertise and infrastructure to advance the development of these state-of-the-art technologies."*[4]

The Simcyp Consortium was formed in 2001 as a collaborative research center for PBPK and mechanistic modeling. Today, 35 biopharmaceutical companies (including all of the top ten global pharma) are members of the Simcyp Consortium. In addition to its industry members, leading academic institutions from around the globe, and key regulatory bodies, including the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Japanese Pharmaceuticals and Medical Devices Agency (PMDA) are affiliates of the Simcyp Consortium. The Consortium members use Certara's Simcyp Simulator to select the most appropriate drug doses, design optimal clinical trials, evaluate new drug formulations, predict drug-drug interactions (DDIs) and PK outcomes in clinical populations, and subsequently inform drug labels.

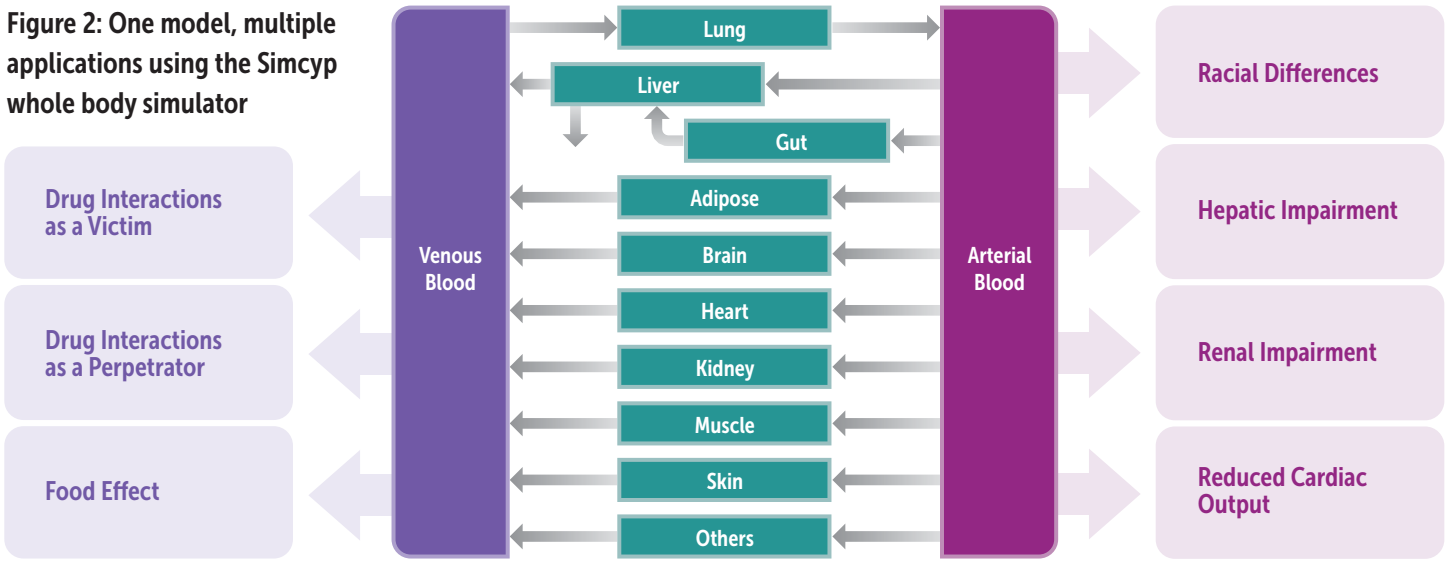
Since its inception, Simcyp has established itself as the vanguard of PBPK and mechanistic modeling and simulation sciences, and the Simcyp Simulator has evolved to become the most sophisticated platform for the prediction of pharmacokinetic outcomes in virtual patient populations.

MYTH BUSTER: The Simcyp Simulator informed nearly 50 novel FDA-approved drugs and over 200 label claims without the need for clinical studies. The documented use of PBPK for drug approvals and other application such as formulation and absorptions has clearly demonstrated how PBPK has become a **regulatory necessity.**

Myth: PBPK is used as a model-fitting tool and not for simulation

Classical modeling approaches, such as pharmacokinetic/pharmacodynamic (PK/PD), and population PK (PopPK) M&S, use clinical data to build "fit for purpose" models tailored to address a specific question and to understand the impact within a clinically circumscribed population. This approach continues to be *essential* in modern drug development. In contrast, mechanistic PBPK modeling starts with a physiological model of the "whole" human population from which clinical population "subsets" may be extracted to explore a myriad of "what if" questions. Certara's Simcyp Simulator maps drug movements in the body to a physiologically realistic compartmental structure using numerous sets of differential equations. The simulator also incorporates anatomical, physiological, and biochemical descriptors of each organ to quantify and predict drug disposition at an organ/cellular level.

Figure 2: One model, multiple applications using the Simcyp whole body simulator



Each tissue is considered to be a physiological compartment with the concentration of the drug in each compartment being determined by combining (biological) systems data, drug data, and trial design (dosing regimen) information. The systems data includes demographic, physiological, and biochemical data for the individuals within the study population of interest. The drug data consists of its physicochemical properties, its (tissue) binding characteristics, and information on its metabolism and the nature of its formulation. The trial design information comprises the dose, administration route, dosing schedule, and co-administered drugs.

The Simulator includes epidemiological, physiological, and genetic databases that facilitate simulating virtual populations with different demographics and ethnicities. This enables predicting drug behavior in virtual patient populations instead of a virtual reference man, allowing individuals at extreme risk to be identified.

PBPK has become an effective tool for a wide range of applications from assessing potential pharmacokinetic differences following a formulation change prior to manufacturing to designing clinical trials and supporting regulatory submissions.[5] Determining safe and efficacious dosing especially for populations at increased risk of medication-related harm, including pediatrics, infants and neonates, geriatrics, pregnant women, those with rare diseases, oncology patients, and patients with impaired organ function, benefit from this technology. So while scientists typically begin with a specific question, the platform is leveraged to answer any number of other questions posed across the development paradigm.

MYTH BUSTER: PBPK is a simulation workhorse at all stages of development. While a model is built for a specific purpose, a simulation can use a model to explore states that would not be originally possible. PBPK's range of capabilities is continually expanding as more systems and drug models are added.

Myth: Commercial PBPK platforms are a scientific "black box"

Those not familiar with commercial PBPK platforms, such as the Simcyp Simulator, may perceive these platforms as a "black box," since the models contained therein cannot be "modified." This is because modeling scientists have traditionally built and modified their own models. According to Dr. Amin Rostami-Hodjegan, Professor of Systems Pharmacology at the Center for Applied Pharmacokinetic Research (CAPKR), University of Manchester, *"Due to the nature and complexity of PBPK—and to ensure consistent and reliable results—PBPK M&S requires a platform that allows the user to 'see' all components of the mechanistic models within, but is sealed from random 'tinkering.'"* In other words, view it as a transparent "secure glass box" where you see the components and algorithms that are used and know exactly how the engine works for each analysis. This transparency allows for the use of many different types of validated and verified models that undergo rigorous testing, providing the consistency and the "quality assured environment" required for regulatory submissions.

PBPK is not a simple one-compartmental pharmacokinetic model, but rather contains hundreds of equations and values that are informing the systems model. From a regulatory perspective, it is critical to control the level of information and number of different elements with strict adherence to established QA, traceability, and audit requirements, including those under FDA's 21 CFR Part 11 requirements.

This "open science" approach and philosophy is leveraged by Simcyp Consortium scientists who contribute to the ongoing development of the Simcyp platform. Working in lockstep with those Consortium members is a team of scientists and developers who, under a peer-review process, qualify, verify, and serve as the "go to" for questions, documents, modifications, and updates, and implement all changes to the platform and models.

MYTH BUSTER: Open science is in a glass box. Using a gated, transparent, qualified, and verified PBPK platform based on open science versus an open source model—which lacks validation and/or version control—delivers the consistency required by regulatory agencies.

Myth: Not enough peer-reviewed PBPK evidence supports regulatory submissions

The use of PBPK models for predicting pharmacokinetics in clinically untested scenarios for drug applications (NDAs, BLAs, ANDAs), regulatory reviews, and post-marketing analyses has escalated in the past several years. A PubMed search for "physiologically-based pharmacokinetics" results in 2,900 publications, 36% published within the past five years. Peer-reviewed publications by subject matter experts are critical in that they provide the "quality control" for determining that the PBPK approach presented is scientifically valid. Publications using Simcyp Simulator include more than 180 published peer-reviewed papers and, since 2007, there are over 300 independent publications applying Simcyp technology, authored by scientists from industry, academia, and regulatory agencies. These publications, including articles, meetings abstracts, reviews, letters, and book chapters, have been cited nearly 6,000 times. These citations cover an ever-increasing range of applications (Figure 4).

Figure 3. The topic of PBPK has seen a steady increase in the leading peer-reviewed journals.

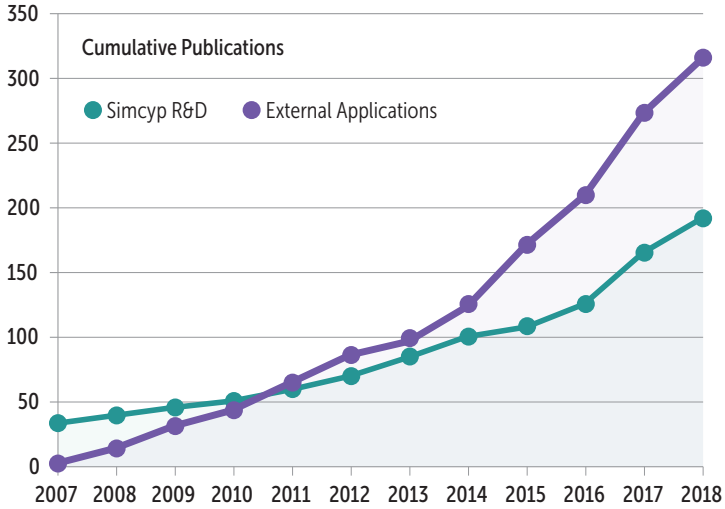
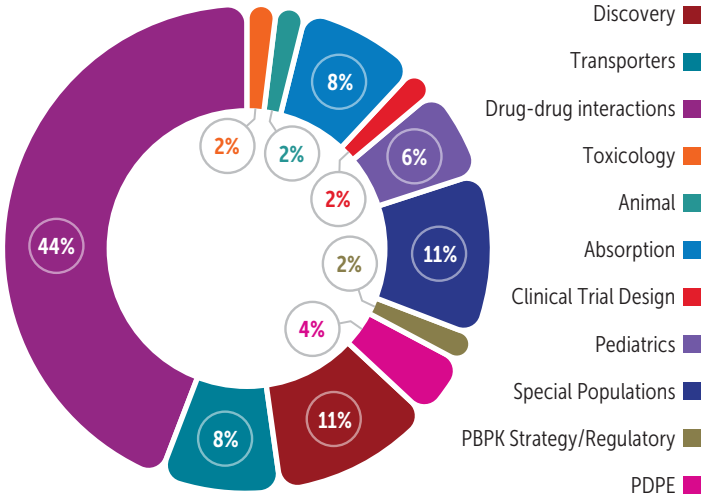


Figure 4. Advancing science of PBPK as demonstrated in a range of subject areas



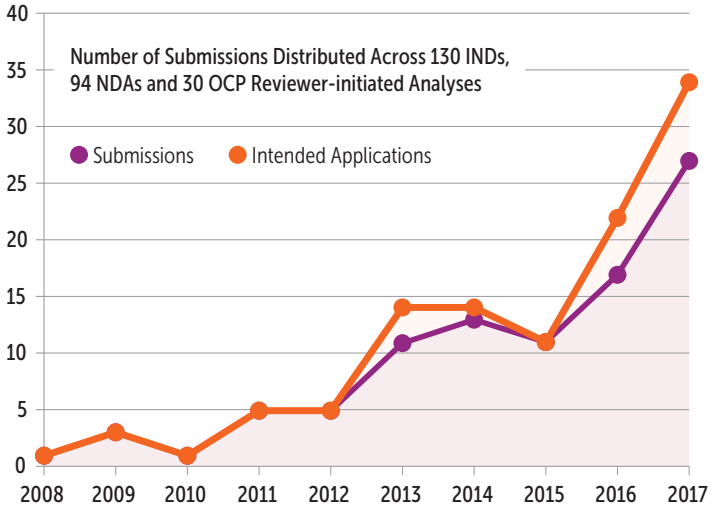
MYTH BUSTER: Simcyp PBPK citations have grown 265% in the past five years. There is rapid rise of prevailing peer-reviewed evidence to demonstrate the benefits of PBPK in drug development. This research unveils a continual advancement and acceptance of this technology for understanding complexities in drug development and explaining those complexities to regulators.

Myth: Regulatory guidance to support PBPK in submissions is lacking

This myth—that there is insufficient clarity from regulators to support PBPK submissions—is far from the truth as the US FDA, the EMA, and the PMDA all recently published PBPK guidelines. These documents give direction to the industry, help streamline the drug approval process, and establish greater consistency and uniformity in PBPK submissions.

In August 2018, the FDA released guidance for reporting PBPK analyses used in regulatory submissions with the goal of facilitating efficient, timely, and consistent review of applications using PBPK.[7] As stated in the FDA guidance, "the decision to accept results from PBPK analyses in lieu of clinical pharmacokinetic (PK) data is made on a case-by-case basis, considering the intended uses, as well as the quality, relevance, and reliability of the results from the PBPK analyses." The final FDA guideline represents feedback provided from pharmaceutical companies, consortiums (including the Simcyp Consortium), regulatory agencies, and individuals. This was followed by similar guidance from EMA, released in December 2018.[8]

Figure 5. 254 total PBPK submissions to the FDA Office of Clinical Pharmacology (OCP)[6]



In 2018, 34 members of the Simcyp Consortium published a comprehensive examination and perspective of the FDA and EMA guidelines. In the paper, the Consortium provided a framework (Figure 6) for PBPK platform qualification, drug model verification, and reporting procedures that sponsors can leverage to expedite regulatory approvals and support critical decision-making.[9] PBPK model development is an iterative process of "predict, learn, and confirm," which is recognized as good practice across various areas of M&S. Model iteration is considered a verification step when new data emerge (ie, clinical observations) and new learnings are applied to the drug model.

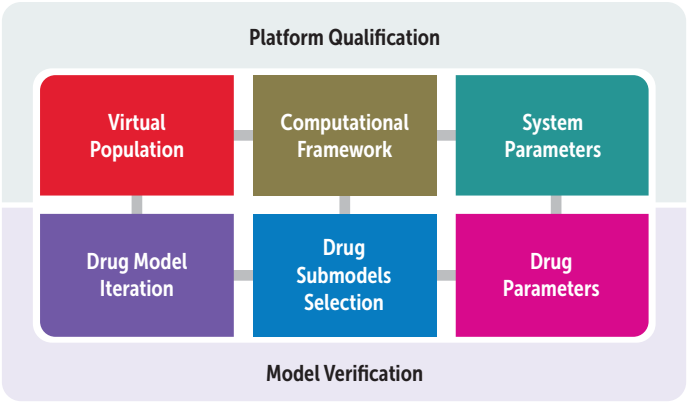


Figure 6: Framework of a PBPK analysis package for regulatory submission

Guidelines proposed by the Consortium include platform qualification, verification of drug models, extending platform qualification processes for various intended uses, examples of PBPK qualification procedures for regulatory submission, templates for reporting analysis plans, and a discussion on challenges and future opportunities. In terms of PBPK platform qualification, the authors differentiate between "qualification" and "verification" of a PBPK platform, whereby qualification refers to a set of prerequisites that ensure permission to handle the intended use, and verification focuses on the predictive performance of the model. Support qualification documentation ensures that the software does as intended to do from a computation perspective. Model verification accounts for consistency between the input parameters and core mechanisms and assumptions within the physiological system and the ability of the model to simulate sets of the observed data.

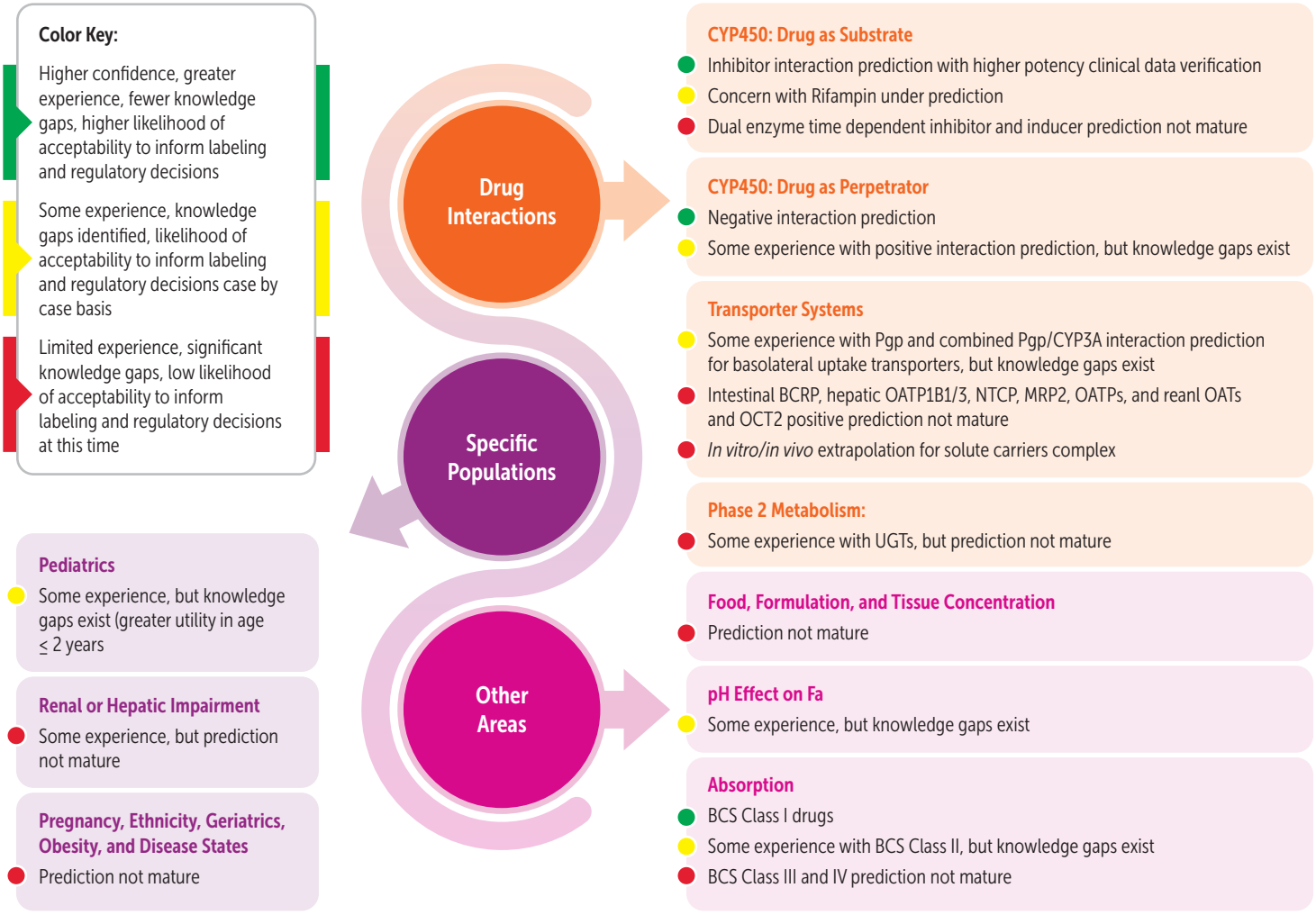
MYTH BUSTER: Guidance from the agencies facilitate the growth in PBPK submission.
The recently released guidance from the FDA and EMA, and its use by PMDA, clearly demonstrate support and direction from regulatory agencies to harmonize reporting, qualification and validation of PBPK models.

Myth: Only high-impact PBPK applications can be used in lieu of clinical studies to inform labels

Regulators require sponsors to submit all clinical study data in advance of market approval, but modeling and simulation data does not have that same requirement. This provides further justification for using modeling and simulation, and specifically PBPK throughout the development process to answer "what if" questions and affirm clinical decision-making. Understanding the value and benefit of that data, regulators are actively encouraging sponsors to engage the agency early in the drug development process and share all virtual clinical study data for discussion during end of Phase 1 and 2 and other face-to-face meetings.

To help guide sponsors, the FDA and EMA recently released decision trees that delineate how they assess data with regards to drug labeling, based on high-, medium-, or low-impact PBPK clinical pharmacology application (Figures 7 and 8).

Figure 7. The predictive performance of high-, medium-, and low-impact PBPK applications for regulatory submissions (FDA)



Source: Grimstein M, et al. (2018). *J Pharm Sci*, Epub ahead of print.

As shown in Figure 7, high impact PBPK analyses have a strong likelihood of acceptability by the FDA when requesting a waiver for clinical studies, to inform drug labels, and to be used in lieu of clinical studies. These applications demonstrate higher confidence, greater experience, and fewer knowledge gaps—the PBPK model has demonstrated very good predictive performance.

Examples of high impact applications using PBPK modeling in lieu of clinical studies include models that predict the impact of weak and moderate index inhibitors on CYP2D6 and CYP3A substrates and the impact of weak and moderate index inducers on CYP3A substrates.

Medium impact applications include the use of PBPK models to predict transporter-based DDIs, BCS Class II, and initial dosing recommendations for clinical trials at the IND stage in pediatric populations. Under this guidance, the FDA is encouraging sponsors to share these complicated applications with them, recognizing that the knowledge base is still evolving. In these cases, the agency may require additional model development by the sponsor, but they are increasingly open to granting waivers where appropriate.

Low impact PBPK analyses are those applications that currently lack the clinical data to verify the model assumptions. These underdeveloped applications which include renal and hepatic impairment, special populations such as pregnancy, ethnicity, geriatrics, obesity, food effects, absorption, Phase 2 metabolism, and others have significant knowledge gaps, and today, have a lower likelihood of acceptability to inform labeling and regulatory decisions.[9] However, proof points are rapidly expanding, and the agency is expected to accept these applications in the future.

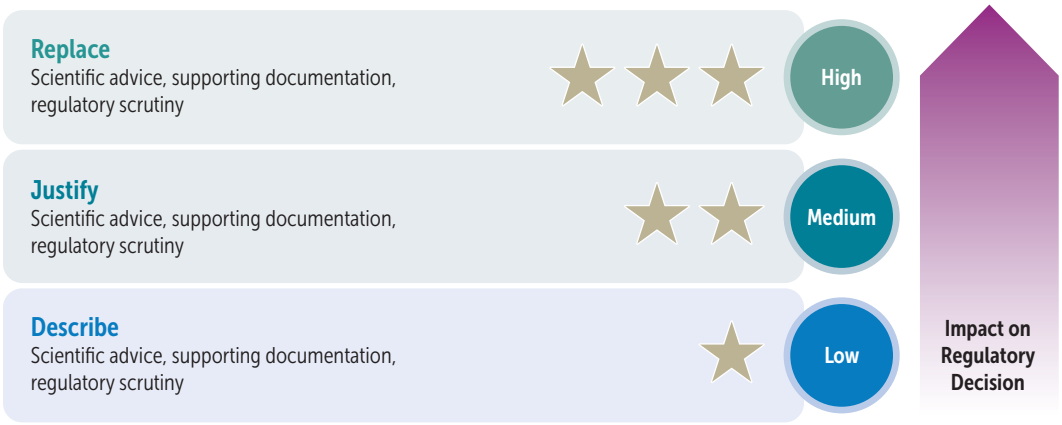


Figure 8. EMA-EFPIA framework for the use of virtual trials in lieu of clinical studies based on regulatory decision impact

Source: EMA-EFPIA Modeling and Simulation Workshop, December 2011

In an effort to standardize M&S approaches/workflows and to establish good practice documentation that reflects the diversity of M&S methods, a framework was proposed during the 2011 EMA-EFPIA Modeling and Simulation Workshop that illustrates "the degree of regulatory scrutiny, level of documentation, and the need for early dialogue that is proportional to the weight or impact of the M&S exercise in regulatory decision making (Figure 8)." Based on the degree of impact, specific regulatory standards are suggested when to use M&S to describe the available evidence base (low impact), to justify the evidence base (medium impact), and to replace the usual evidence base (high impact).[10]

MYTH BUSTER: Sharing PBPK data with the agency early increases the chance for waivers.
Discuss PBPK analysis data with regulators early in the drug development process and submit all virtual clinical study data. This will provide a better understanding by sponsors and regulators of the predictive performance of PBPK models for all applications, presently, and in the future.

Myth: PBPK modeling is too complex

There is an ongoing debate within the scientific community about the value of using static versus dynamic PBPK models. According to Dr. Rostami-Hodjegan, *"both types of models provide similar answers to a singular question posed 'today,' but only dynamic models can answer questions posed both today and in the future."*

For example, dynamic PBPK modeling provides benefits for optimizing study design to maximize the chance of success, understanding drug performance in special populations, developing new formulations, and how to stagger dosing with food (food effect), ie, the one model can answer multiple questions. In contrast, a static modeling approach would require multiple models to answer each of these questions. Take for example static versus dynamic digestion models. Static models mainly function to mimic the biochemical processes in the gastrointestinal (GI) tract usually using a single set of initial conditions (eg, pH, bile salts, and enzyme concentrations) for each part of the GI tract. This simplistic approach does not often provide a realistic simulation of the more complex, ever-changing *in vivo* conditions that can be achieved with more complex dynamic models.

Dynamic models support the argument "you don't know what you can achieve by different simulation unless you build the model." Then you can use the model to start to ask many different questions, eg, "What happens with a high fat versus low fat meal?" or "How does a standard FDA breakfast compare to a non-standard European breakfast?" A static model will not give you the answers to these types of questions.

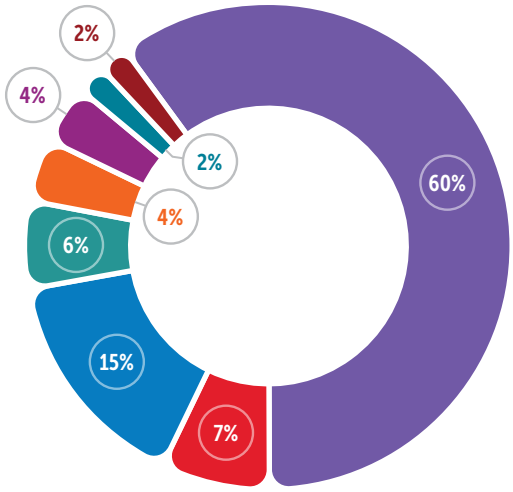
MYTH BUSTER: Dynamic models answer current and future questions. Dynamic models are sophisticated and contain details that may not be needed to answer immediate questions, but can be used to support future studies in a wide range of development topics.

Myth: PBPK is only useful for predicting drug-drug interactions (DDIs)

Although early regulatory submission of PBPK analyses were predominantly used to predict DDIs, it has been demonstrated that applications are steadily expanding into other areas, including drug formulation and/or absorption modeling, age- and ethnic-related changes in PK and disposition, and assessment of PK changes associated with pathophysiological conditions such as hepatic and renal impairment.

Figure 9. Distribution of PBPK application areas in IND/NDA submissions to the FDA

Source: Grimstein M. et al. (2018). *J Pharm Sci,* Epub ahead of print.



The PBPK regulatory submission data shown in Figure 9 compares to that observed by the Certara PBPK consultancy scientists, who have supported hundreds of projects. Although many projects encompass enzyme-mediated DDIs, including complex Cyp3A4/P-glycoprotein (Pgp) drug-drug interactions, pH-dependent DDIs (an increasing challenge in particular for oncology drugs), there is an increase in the number of other types of PBPK applications, many related to regulatory queries, including transporter-mediated DDIs, pediatric dose extrapolation, formulation effects, first-in-human dose extrapolation, and other routes of administration. While, historically, most of the PBPK analyses are at the interface between early and late development, there has been an increase in discovery-type projects, further demonstrating PBPK's value.

It is expected that further development of PBPK models, and their regulatory impact on other areas of clinical application, will continue to expand. A further spurt of growth will come from greater interoperability between PBPK and other platforms such as QSP models of disease progression, and those supporting precision dosing within the clinical/hospital environment. Evidence of PBPK modeling trends has been documented for applications, including evaluation of drug disposition in kidney, brain, and lung, and antibody drug conjugate disposition.[11,12]

Supporting these observations are trends seen in Simcyp journal articles published from 2017–2018, which demonstrate a significant shift in the use of PBPK in areas other than DDIs (Figure 10).

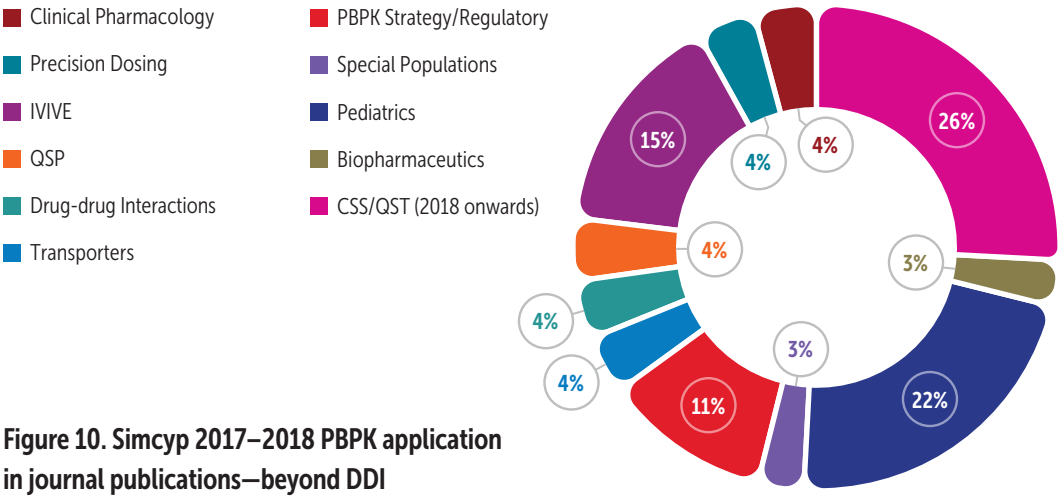


Figure 10. Simcyp 2017–2018 PBPK application in journal publications—beyond DDI

MYTH BUSTER: DDI success sets the stage for expanded PBPK acceptance. As seen in regulatory submissions, and observed in the literature, PBPK applications are expanding beyond the prediction of DDIs to other areas such as drug formulation and/or absorption modeling, age- and ethnic-related changes in PK and disposition, and assessment of PK changes associated with pathophysiological conditions such as hepatic and renal impairment.

Myth: PBPK is only for small molecules, not biologics

PBPK is well established as a mechanistic approach to predict the PK of small molecules using laboratory-derived data, however it is being increasingly used in biologic drug development. Protein-based therapeutic drugs comprise monoclonal antibodies (mAbs), vaccines, recombinant hormones, antibody-drug conjugates, RNAi, antisense, blood factors, and other large molecules.

Substantial advances in the fields of genomics, proteomics, metabolomics, bioinformatics, and other disciplines, combined with improved technologies and tools for biomedical analysis and diagnoses, have made a significant impact on biologic drug development. Biologics offer the potential for high efficacy with fewer side effects. This has led to a discernable rise in biologic drug development programs which represent greater than 50% of drug candidates in development and new drug approvals, particularly for oncological, rare autoimmune, and neurological diseases.

Although the development of PBPK models for therapeutic proteins (TP) is advancing, and their role in drug development is still being evaluated, there is growing confidence in their ability to predict the human PK behavior of TPs and add to the understanding of the mechanisms of absorption, distribution, and elimination of these complex drugs.[13]

The Simcyp Simulator can simulate mAB PK in humans using a mechanistic minimal PBPK model where the body is divided into three compartments: plasma, tissue, and lymph, with the tissue compartment being further subdivided into vascular, endothelial, and interstitial space. The model can account for levels of both endogenous IgG and exogenous therapeutic mAbs in each compartment and sub-compartment. Further, with PBPK considered a key component of pediatric drug development, Simcyp Pediatric—a module within the Simcyp Simulator—allows PK modeling in neonates, infants, and children. The Simcyp Simulator's pediatric biologics module allows user-defined IgG catabolic and systemic clearance ontogeny profiles for large molecules, providing valuable information for first-time dosing decisions and the design of pediatric clinical studies.

PBPK models have been developed to predict absorption rates of TPs following subcutaneous (SC) dosing, which with future model enhancements to predict distribution at the injection site and through the interstitial space, and pre-systemic elimination, will provide a true bottom-up approach to predict TP SC absorption.[14]

MYTH BUSTER: PBPK can be used for both small molecule and biologic drug development. A PBPK approach to TP drug development has the ability to account for mechanisms responsible for biologic drug disposition, help bridge pre-clinical to clinical studies to simulate dosing outcomes, and account for altered physiology in disease states and assess their impact on PK. Continued exploration and characterization of biologic drug PK using PBPK modeling will help bring safer, more efficacious treatments to market.

Myth: PBPK has not been applied to predict PK in real patients (model-informed precision dosing)

The use and value of PBPK in drug development is well established, however as it pertains to model-informed precision dosing (MIPD), can a PBPK approach to MIPD transition from an "academic nicety" to a "clinical reality?" MIPD is a modeling and simulation approach that is used to predict the most effective and/or least toxic drug dose for an individual patient. MIPD could revolutionize healthcare by reducing the incidence of adverse drug reactions (ADRs), improving drug efficacy and increasing patient adherence. Precision dosing in clinical medicine is needed for drugs with a narrow therapeutic index (eg, anti-arrhythmics, anti-coagulants, anti-epileptics, anti-neoplastics, aminoglycoside antibiotics, immunosuppressants) and drugs with very wide interpatient PK/PD variability. Populations at increased risk of medication-related harm also benefit from MIPD, including pediatrics, infants and neonates, geriatrics, pregnant women, those with rare diseases, oncology patients, and patients with impaired organ function.[5]

In May 2016, key opinion leaders in clinical, academia, industry, and legal/regulatory met at a Healthcare Summit in Cheshire, UK to present 16 MIPD case studies and to discuss the opportunities and challenges of MIPD and the steps needed for it to become a clinical reality.[15] A follow-up meeting was held in Busan, South Korea in December 2017.[16] During these meetings, the patient, disease, and drug characteristics which describe the areas where MIPD has high potential impact for dose optimization were proposed (Figure 11).

Examples of potential high-impact MIPD scenarios where the evidence is being collected include the treatment of resistant schizophrenia (clozapine initiation), getting the anti-coagulant dose right in patients with atrial fibrillation, atomoxetine dosing in children with ADHD, and treatment of solid tumors and hematological malignancies (kinase inhibitor initiation and titration).

Speakers at both meetings also highlighted case studies where MIPD has been used in clinical practice, including DDIs and HIV treatment, oncology, infectious diseases, pediatric dose adjustments, and dosing in special populations (pregnant women, renal transplant recipients, heart failure patients, obesity and post-bariatric surgery patients).

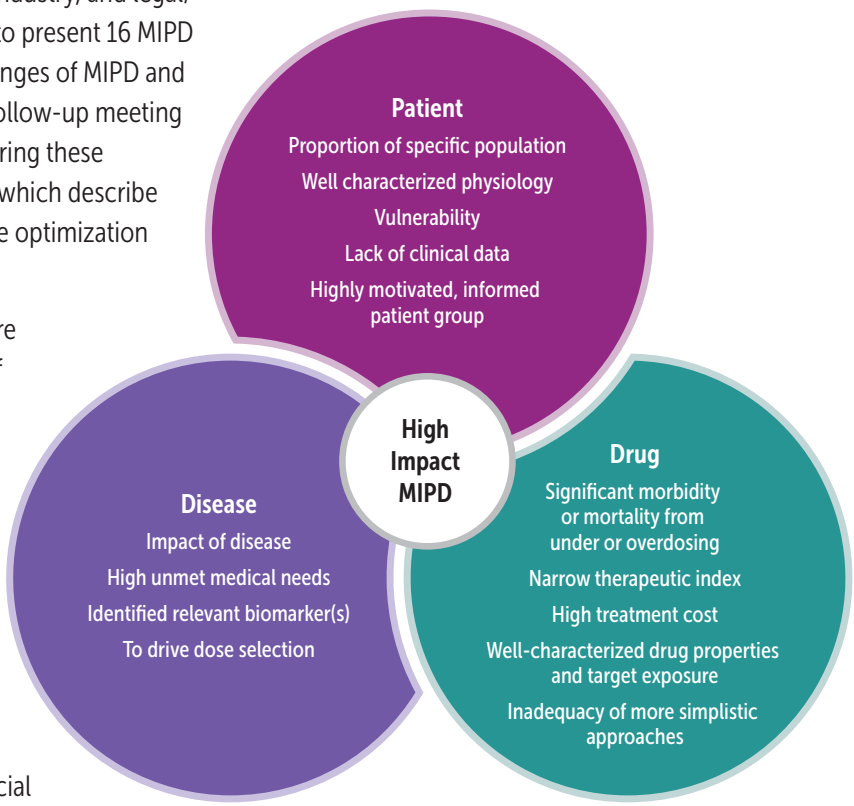


Figure 11. Patient, disease, and drug characteristics that collectively indicate a high impact MIPD case

Source: Darwich AS, et al. (2017). *Clin Pharmacol Ther, 101*(5), 646–656.

Recent publications have started to use the Simcyp Simulator Virtual Twin Technology to predict pharmacokinetics in real patients. The Virtual Twin™ Technology simply adapts some of the biological and physiological data used to build a base PBPK model representative of the population with individual information about these parameters that better matches the patient, eg, specific renal, liver, and cardiac function, hematocrit, DMET genotype and phenotype.

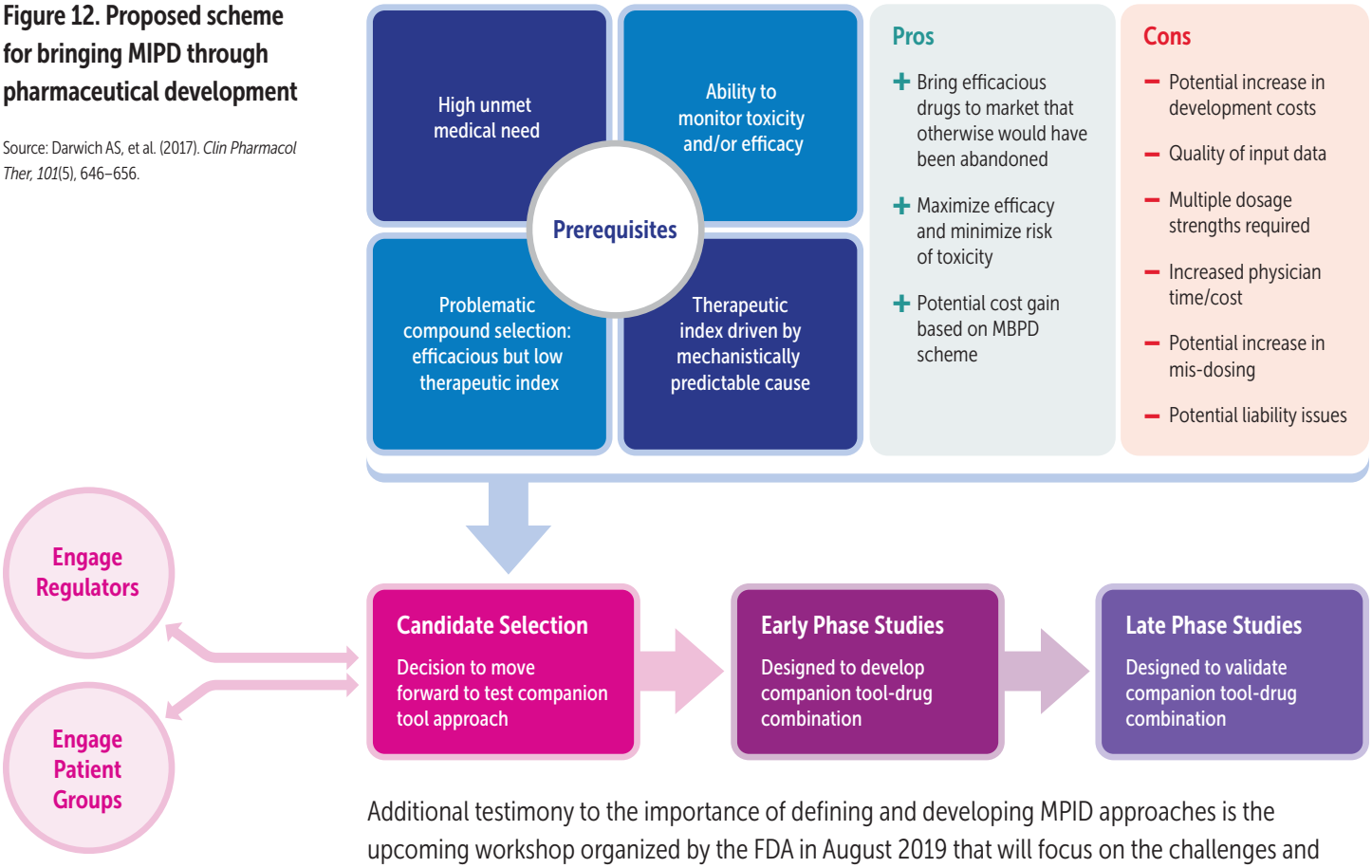
These publications showed that (1) the olanzapine systemic exposure could be predicted in Virtual Twins when compared to actual drug concentrations in the corresponding patients,[17] and (2) an *in silico* quantitative systems toxicology (QST) model linked to PBPK for citalopram could predict the likely occurrence of cardiotoxic events in real patients under different clinical conditions.[18]

The concept of co-development of a companion PBPK MIPD dosing tool in drug development has been recently further evaluated as a key strategy to accelerate clinical implementation of MIPD.[19] The proposal for the co-development of MIPD tools "implemented by a universal platform designed at a pre-competitive stage that generates virtual twins of patients suitable for dose prediction," will aid in accelerating MIPD into clinical medicine. A drug that is developed with MIPD companion tools would be prescribed with the assistance of the tools. The tool, which focuses on high impact MIPD, particularly drugs with narrow therapeutic indexes, would create a strong business case for sponsors, regulators, providers, clinicians, and most importantly, patients. These advantages include, for example, improving clinical trial success, facilitating the development of problem drugs where traditional approaches have been unsuccessful, creating a value- or outcome-based business environment that would incentivize manufacturers to find the best dose and to find the best patients that would benefit the most, and improving the quality of prescribing information, among others.

The following figure shows aspects to be considered for bringing MIPD through drug development.

Figure 12. Proposed scheme for bringing MIPD through pharmaceutical development

Source: Darwich AS, et al. (2017). *Clin Pharmacol Ther, 101*(5), 646–656.



Additional testimony to the importance of defining and developing MPID approaches is the upcoming workshop organized by the FDA in August 2019 that will focus on the challenges and opportunities for MIPD. This indicates how regulators understand the potential benefits that MIPD can have for patients and healthcare systems.

MYTH BUSTER: PBPK is transitioning from R&D to clinical practice. MIPD using a PBPK approach holds great promise to revolutionize healthcare in being able to provide the right drug dose to maximize therapeutic benefit, while reducing risk for each individual patient. The co-development of MIPD companion tools and increased involvement of regulators will help accelerate the implementation of MIPD in clinical medicine.

The Future of PBPK Modeling

As highlighted in a 2017 edition of AAPS Newsmagazine, PBPK can be considered the Swiss Army knife of M&S. PBPK is being used for a wide range of applications to support regulatory submissions and streamline drug development. In recent years PBPK modeling has become an established and steadfast approach used by sponsors, regulators and academics. The increase in PBPK regulatory submissions, the release of agency guidance to harmonize and support PBPK submissions, and continued advances in PBPK applications, such as precision dosing in individual patients, are a testimony to the importance and regulatory necessity of this powerful mechanistic modeling approach. PBPK and mechanistic modeling have a bright future!

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