MINI REVIEWS

The Utility of Modeling and Simulation in Drug Development and Regulatory Review

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ABSTRACT: US Food and Drug Administration (FDA) has identified innovation in clinical evaluations as a major scientific priority area. This paper provides case studies and updates to describe the efforts by the FDA's Office of Clinical Pharmacology in its development and application of regulatory science, focusing on modeling and simulation. Key issues and challenges are identified that need to be addressed to promote the uptake of modeling and simulation approaches in drug regulation. Published 2013. This article is a U.S. Government work and is in the public domain in the USA. 102:2912–2923, 2013

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INTRODUCTION

One important aspect of the United States Food and Drug Administration (US FDA)'s mission is to make drug therapies available to the American public in a timely manner. In its recent efforts to foster efficient and informative drug development, the US FDA has made priorities of promoting biomedical innovation, early communication with drug developers, and administrative and scientific flexibility.[1] The US FDA approved 35 new molecular entities in fiscal year 2012. Approvals included groundbreaking treatments for a variety of unmet medical needs. (Table 1) Additionally, many of these therapies were developed, evaluated by US FDA, and/or approved via expedited mechanisms. Despite these successes, there have been intermittent calls to reform the drug development and regulatory enterprises (Ref. [2] and references therein). Provisions in the recently enacted US FDA Safety and Innovation Act (FDASIA)[3] and the reauthorized Prescription Drug User Fee Act V (PDUFA V) underscore the need for and importance of developing new approaches to streamline drug development and regulatory evaluation. Various public–private partnerships have been formed under the "critical path initiatives"[4,5] to improve the exchange of innovations and information about drug development among the US FDA, industry, academic scientists, and patient advocacy groups. A recent update on these activities has shown results of leveraging collaborations in regulatory science.[6]

The United States Food and Drug Administration continues to target improvements in regulatory science, including the development of scientific tools that can bridge the gap between cutting-edge discoveries and real-world diagnostics and therapeutics. US FDA has identified innovation in clinical evaluations (e.g., through modeling and simulation) as a major scientific priority area.[7] US FDA's Office of Clinical Pharmacology (OCP) has used modeling and simulation strategies to address a variety of drug development, regulatory, and therapeutic questions over the past decade.[8–11] Notwithstanding, the science of quantitative clinical pharmacology continues to advance at a rapid pace such that regulators must constantly evaluate the most appropriate applications of modeling, simulation, and other innovations in the public health context.[2]

In this paper, we discuss recent efforts by the US FDA's OCP in the development and application of regulatory science focusing on modeling and simulation. Case studies and updates are provided to illustrate (1) the impact of pharmacometric analyses on the premarket approval and labeling of new drugs and the application of accumulated regulatory experience to the review of investigational new drugs (INDs),

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Table 1. New Molecular Entities Approved in Fiscal Year 2012 (October 2011 to September 2012) by the US FDA (from the US FDA FY2012 Innovative Drug Approvals Report: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM330859.pdf)

Drug Name	Approval Date	Indication	Orphan Drug	Approved First in USA	PDUFA Date Met	Approved First Cycle	Sponsor
I. Priority Drugs							
AMYVID (florbetapir F18)	April 6, 2012	To estimate beta-amyloid plaque density in brains of patients with cognitive impairment		√	√		Avid Radio- Pharmaceuticals, Inc., Philadelphia, Pennsylvania
CHOLINE C 11	September 12, 2012	For PET imaging of suspected prostate cancer hce		NA	√	√	Mayo Clinic PET Radiochemistry Facility, Rochester, Michigan
ERIVEDGE (vismodegib)	January 30, 2012	For advanced basal cell carcinoma		√	√	√	Genentech, Inc., South San Francisco, California
ERWINAZE (asparaginase erwinia chrysanthemi)	November 18, 2011	For patients with acute lymphoblastic leukemia (ALL) and allergy to *E. coli*-derived asparaginase and pegaspargase chemotherapy drugs	√			√	EUSA Pharma (USA), Inc., Langhorne, Pennsylvania
EYLEA (aflibercept)	November 18, 2011	For wet, age-related macular degeneration		√	√	√	Regeneron Pharmaceuticals, Inc., Tarrytown, New York
JAKAFI (ruxolitinib)	November 16, 2011	For the bone marrow disease myelofibrosis	√	√	√	√	Incyte Corporation, Wilmington, Delaware
KALYDECO (ivacaftor)	November 31, 2011	For cystic fibrosis patients with G551D mutation	√	√	√	√	Vertex Pharmaceuticals, Inc., Cambridge, Massachusetts
PERJETA (pertuzumab)	June 8, 2012	For HER2-positive metastatic breast cancer		√	√	√	Genentech, Inc., South San Francisco, California
STIVARGA (regorafenib)	September 27, 2012	For metastatic colorectal cancer		√	√	√	Bayer Healthcare Pharmaceuticals, Inc., Wayne, New Jersey
VORAXAZE (glucarpidase)	January 17, 2012	To treat toxic methotrexate concentrations in plasma of patients receiving chemotherapy	√	√	√	√	Btg international, Inc., West Conshohocken, Pennsylvania
XTANDI (enzalutamide)	August 3, 2012	For metastatic, castration-resistant prostate cancer		√	√	√	Medivation, Inc., South San Francisco, California
ZALTRAP (ziv-aflibercept)	August 3, 2012	For metastatic colorectal cancer		√	√	√	Sanofi-Aventis U.S., llc, Bridgewater, New Jersey
II. Standard Drugs							
AUBAGIO (teriflunomide)	September 12, 2012	For relapsing forms of multiple sclerosis (MS)		√	√	√	Sanofi-Aventis, U.S., llc.
BElVIQ (lorcaserin hydrochloride)	June 27, 2012	For chronic weight management		√	√		Arena Pharmaceuticals, Inc., Zofingen, Switzerland
BOSULIF (bosutinib)	September 4, 2012	For chronic myelogenous leukemia (CML)	√	√	√	√	Pfizer Inc., New York City, New York
ElElYSO (taliglucerase alfa)	May 1, 2012	For type-1 gaucher disease, a rare genetic disorder	√	√	√		Protalix Biotherapeutics Inc., Carmiel, Israel

continued

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Table 1. Continued.

Drug Name	Approval Date	Indication	Orphan Drug	Approved First in USA	PDUFA Date Met	Approved First Cycle	Sponsor
FERRIPROX (deferiprone)	October 14, 2011	For iron overload in patients with thalassemia (a genetic disorder causing anemia)	√		√		Apopharma, Inc., Toronto, Canada
GINTUIT (allogeneic cultured keratinocytes and fibroblasts in bovine collagen)	March 9, 2012	For application to vascular wound beds in the treatment of mucogingival conditions		√	√	√	Organogenesis, Inc., Canton, Massachusetts
HEMACORD (hemapoietic progenitor cells, cord (HPC-C)	November 10, 2011	For use in unrelated donor hematopoietic progenitor cell transplantation in patients with certain blood disorders		NA	√	√	New York Blood Center, Inc., New York City, New York
HPC, Cord Blood (hemapoietic progenitor cells, cord (HPC-C)	May 24, 2012	For use in unrelated donor hematopoietic progenitor cell transplantation in patients with certain blood disorders		NA	√	√	Clinimmune Labs, Aurora, Colorado
INLYTA (axitinib)	January 27, 2012	For advanced kidney cancer		√	√	√	Pfizer, Inc., New York City, New York
KYPROLIS (carfilzomib)	July 20, 2012	For multiple myeloma	√	√	√	√	Onyx Pharmaceuticals, Inc., South San Francisco, California
LINZESS (linaclotide)	August 30, 2012	For irritable bowel syndrome with constipation (IBS-C)		√	√	√	Forest Laboratories, Inc., St. Louis, Missouri
MENHIBRIX (Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine)	June 14, 2012	Combination vaccine to prevent meningococcal disease and Haemophilus influenzae type b (Hib) in children		√	√		GlaxoSmithKline Biologicals, based in Rixensart, Belgium
MYRBERTIQ (mirabegron)	June 28, 2012	For treatment of overactive bladder			√	√	Astellas Pharma Global Development, Inc., Northbrook, Illinois
NEUTROVAL (tbo-filgrastim)	August 29, 2012	To reduce duration of neutropenia in chemotherapy patients			√		Sicor Biotech UAB Vilnius, Lithuania
OMONTYS (peginesatide)	March 27, 2012	For anemia in chronic kidney disease patients on dialysis		√	√	√	Affymax, Inc., Palo Alto, California
ONFI (clobazam)	October 21, 2011	For seizures associated with Lennox-Gastaux syndrome	√		√	√	Lundbeck, Inc., Deerfield, Illinois
PICATO (ingenol mebutate)	January 23, 2012	For the topical treatment of actinic keratosis		√	√	√	Leo Pharma AS, Ballerup, Denmark
PREPOPIK (sodium picosulfate, magnesium oxide, citric acid)	July 16, 2012	For colon cleansing in preparation for colonoscopy			√	√	Ferring Pharmaceuticals Parsippany, New Jersey

continued

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Table 1. Continued.

Drug Name	Approval Date	Indication	Orphan Drug	Approved First in USA	PDUFA Date Met	Approved First Cycle	Sponsor
STENDRA (avanafil)	April 27, 2012	For the treatment of erectile dysfunction (ED)			√	√	Vivus Inc., Mountain View, California
STRIBILD (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate)	August 27, 2012	For treatment of HIV-1		√	√	√	Gilead Sciences, Inc., Foster City, California
SURFAXIN (lucinactant)	March 6, 2012	To prevent respiratory distress syndrome (RDS) in premature infants		√	√		Discovery Laboratories, Inc., Warrington, Pennsylvania
TUDORZA PRESSAIR (aclidinium bromide)	July 23, 2012	For long-term maintenance treatment of bronchospasm in COPD		√	√	√	Forest Laboratories, Inc., St. Louis, Missouri
ZIOPTAN (tafluprost)	February 10, 2012	To reduce intraocular pressure (IOP) in patients with glaucoma or ocular hypertension			√		Merck Sharp and Dohme Corporation, Whitehouse Station, New Jersey

(2) the potential for physiologically based pharmacokinetic (PBPK) modeling to address questions related to individualization of doses based on patient-specific factors (e.g., age, sex, race, organ dysfunction, concomitant drug administration), and (3) required processes for the development of predictive safety tools employing preclinical, *in vitro*, and *in silico* methods using the vast US FDA database and other "precompetitive" information with collaborations from multiple internal and external parties.

PHARMACOMETRIC MODELING

The utility of modeling and simulation in drug development and regulatory review has been well documented.[10,12] Among the many applications, most of the OCP efforts have been focused on late phase decisions such as dosing and labeling or postapproval evaluation of unstudied doses or dosing regimens.[10,11] Recently, we have increased efforts to apply modeling and simulation to assist in dose selection and trial design for late phase trials based on data obtained from early phase clinical trials. Three case studies are highlighted below to illustrate the application of pharmacometric analyses to address two major challenges: dose optimization and extrapolation of therapeutic effect to unstudied populations.[13–18] The models applied in our evaluation are listed in Table 2.

Dose Optimization—Experience from Trastuzumab for Metastatic Gastric Cancer

Dose optimization has not been the focus of oncology drug development until recent years. Insufficient selection of dose and dosing schedule is one of the many reasons that could be related to the low success rates in oncology drug development programs in which dose-ranging trials to optimize dose selection for efficacy are rarely conducted. In the absence of activity-based, dose-ranging studies, exposure–response (E–R) analyses of data from "pivotal" efficacy trials may aid in dose refinement and/or risk/benefit evaluation; here, we present one such example.

Trastuzumab was initially approved by the US FDA in 1998 for metastatic HER2-overexpressing breast cancer. In 2010, the US FDA approved trastuzumab for HER2-overexpressing metastatic gastric cancer (mGC). In the phase 3 trial for trastuzumab for mGC, the same dosing regimen approved for breast cancer was chosen for the new patient population. During the regulatory review, an analysis based on clinical data obtained from this phase 3 trial, which employed one dose level, was conducted to assess whether the proposed dosing regimen was supported by the E–R relationship. Because of the nonrandomized nature of this E–R analysis, there were multiple confounding factors. To address this, an additional case–control analysis was

Table 2. Models Used in Three Cases Presented Under the "Pharmacometric Modeling" Section

	Trastuzumab	Boceprevir/telaprevir	Topiramate
Model	Compartmental pharmacokinetic model for exposure and statistical models (Cox model and case–control analysis) for exposure–response analysis	Mathematical models for proportions in subgroups of a population	Compartmental pharmacokinetic model

conducted to minimize the bias in the estimation of the treatment effect at a certain exposure level. The matched factors included Eastern Cooperative Oncology Group Performance Score, prior gastrectomy, number of metastatic sites, Asian ethnicity, and immunohistochemistry.[13] The pharmacometric analysis suggested that patients in the lowest quartile of trastuzumab trough concentrations were at significant risk of treatment failure (as measured by decreased overall survival). These patients could be subject to known serious toxicities of trastuzumb without the benefits from the trastuzumab treatment. As a result of the pharmacometric analysis, several postmarketing requirement (PMR) studies were requested of the sponsor to conduct further evaluations, including one trial to evaluate alternate (higher or individualized) dosing regimens.[14] This type of pharmacometric analysis, if conducted early during drug development, may help optimize patient dose and improve the success rate of phase 3 trials of oncology drug products.

Extrapolation of Indications to Unstudied Patient Group—Boceprevir and Telaprevir for Chronic Hepatitis C

Chronic hepatitis C is a major cause of cirrhosis in North America. Before the US FDA's approval of boceprevir and telaprevir in May 2011, the standard of care for chronic hepatitis C was peginterferon alfa in combination with ribavirin for 48 weeks. Traditionally, patients with chronic hepatitis C are divided into two broad categories (treatment naive and treatment experienced) based on their previous exposure to interferon-based therapy. Treatment experienced subjects who failed the previous round of peginterferon/ribavirin treatment are further classified into relapsers, partial responders, and null responders.

Boceprevir and telaprevir are hepatitis C virus (HCV) NS3/4A protease inhibitors and represent a new class of small molecules that directly targets virus replication. Despite the convincing efficacy results of both drugs in treatment-naive patients, there were still considerable concerns about the efficacy and the optimal doses in the treatment-experienced and a subgroup of treatment-naive patients.[15] Unresolved questions addressed in the boceprevir and telaprevir reviews included: (1) Is there evidence of boceprevir effectiveness for prior null responders with peginterferon/ribavirin (a subgroup that was specifically excluded from the pivotal study)? (2) What is the appropriate boceprevir dosing regimen for a subset of treatment-naive subjects who are late responders?, and (3) Can telaprevir response guided therapy, which can shorten the treatment duration from 48 weeks to 24 weeks in >60% of the treatment-naive patients, be approved in prior relapsers with peginterferon/ribavirin (a group in which response guided therapy was not prospectively evaluated). To address these challenging questions, multiple additional clinical trials would typically be required by US FDA to gather additional information. However, a novel pharmacometric method[16,17] was applied in the review process to quantitatively bridge knowledge between treatment naive and experienced patients when information was lacking in one population. Detailed description of the method is described in separate papers.[16,17] This analysis demonstrated that interferon responsiveness for a second course of peginterferon/ribavirin treatment did not change after the first course of treatment. This novel pharmacometric method was presented at both boceprevir and telaprevir Advisory Committee meetings and the analyses served as the foundation for the following US FDA decisions on telaprevir and boceprevir: (1) the effectiveness of boceprevir for the unstudied treatment-experienced subgroup can be established from available data in treatment-naive patients; (2) the appropriate boceprevir dosing regimen for treatment-naive subjects who are late responders was established based on data from treatment-experienced patients; and (3) telaprevir response guided therapy can be approved in a subgroup that was not studied in the trials. The approval of these two new drugs for HCV patients with appropriate dosing regimens provided the timely benefit to all HCV patients and avoided delay and suboptimal dosing regimen in certain subgroups.

Extrapolation of Indications to Specific Pediatric Patients—Topiramate for Epilepsy

Anticonvulsants are generally studied and approved initially for adjunctive use as such clinical efficacy trials can be readily performed. However, subsequent clinical trials for monotherapy present particular experimental and ethical challenges, especially for pediatric patients. Therefore, alternative methods are needed to substantiate the approval decision and to identify the appropriate dosing regimen for monotherapy in pediatrics.

Topiramate has been approved for adjunctive therapy in adults and in children 2 years and older based on phase 3 trials. It is also approved for monotherapy to treat partial onset seizures and primary generalized tonic–clonic seizures in adults and children 10 years and older based on phase 3 trials. Efficacy data for monotherapy in pediatrics 2–10 years old could not be obtained from clinical efficacy trials. A pharmacometric method was developed and applied to quantitatively bridge knowledge between adults and pediatrics in monotherapy and adjunctive therapies. This approach consisted of first showing a similar E–R relationship between adults and pediatric patients 2 years and older when topiramate was given as an adjunctive therapy. Next, the similarity of the E–R relationships was demonstrated in adults and pediatric patients ages 6 to <16 years when topiramate was given as initial monotherapy. Specific dosing in children 2 to <10 years of age was then derived from simulations utilizing plasma exposure ranges observed in pediatric and adult patients treated with topiramate in monotherapy. The above analyses made it possible to extrapolate monotherapy efficacy from patients 10 years and older to pediatric patients 2 to <10 years old by matching the topiramate exposures in these pediatrics to exposures observed in adults and older pediatric patients. The safety data obtained in the relevant pediatric patients given at a higher dose level of topiramate was used to ensure that the targeted topiramate exposure is within the "safe" exposure range. Because of the limited strengths of topiramate tablet (the lowest strength is 25 mg), an additional optimization algorithm was implemented to individualize the dosing regimen to target the desired topiramate exposure as closely as possible for each pediatric patient. This individualized dosing regimen was approved for topiramate pediatric monotherapy.[18]

PBPK MODELING

Physiologically based pharmacokinetic modeling has been used extensively in the past in the estimation of human exposure of environmental chemicals. Recent advancement in the understanding of physiological and biological processes, drug disposition including drug transport,[19] and computer science, coupled with the availability of several specialized PBPK software packages, has contributed to more widespread use of PBPK in drug discovery, drug development, and regulatory review. PBPK has been applied for early *in vitro* to *in vivo* predictions of the PK of investigational drugs in first-in-human studies[20,21] and for the evaluation of the effects of intrinsic and extrinsic factors, alone or in combination, on drug exposure.[22,23] Between 2008 and 2012, the US FDA received 33 IND/NDA (Investigational New Drug/New Drug Application) submissions containing PBPK modeling approaches. In parallel with the increasing number of submissions containing PBPK, the agency has increasingly utilized de novo (i.e., US FDA initiated) PBPK in its reviews to help characterize PK in a variety of complex clinical scenarios. Figure 1 shows the number of submitted IND/NDA containing PBPK, and the number of models developed by OCP during its regulatory review from 2008 to 2012. The following cases illustrate application of PBPK to inform several decisions related to therapeutic use from a regulatory standpoint (Fig. 2).

Drug–Drug Interactions

Case 1—Focused Clinical Drug Interaction Studies Based on in Vitro Inhibition Data

Cabazitaxel is approved for hormone-refractory metastatic prostate cancer. Although *in vitro* data suggested that it could inhibit CYP3A, a PBPK

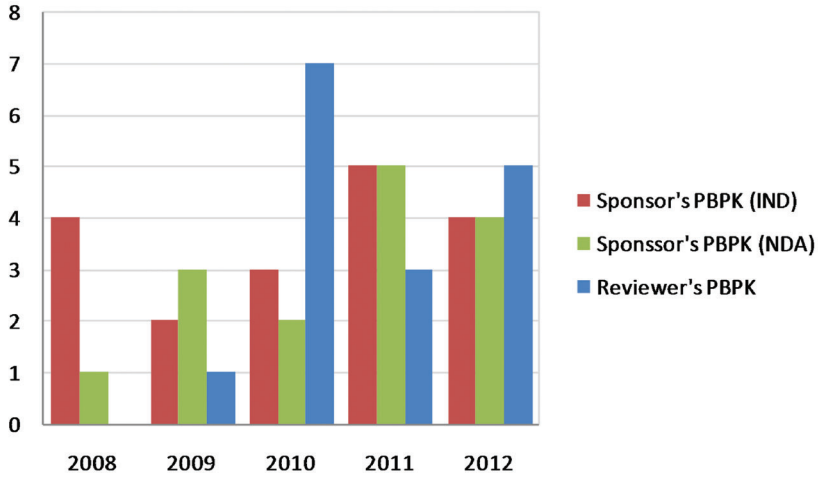


Figure 1. The number of PBPK applications contained in IND/NDA submissions or developed by US FDA reviewers from 2008 to 2012.

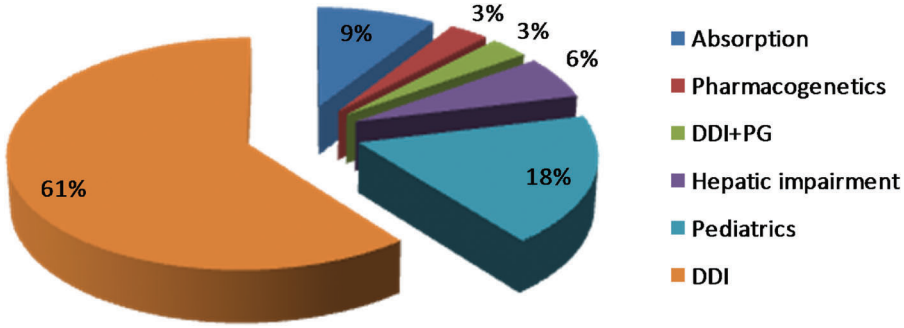


Figure 2. Areas of applications in the 33 PBPK submissions in IND/NDA received by US FDA's Office of Clinical Pharmacology from 2008 to 2012.

analysis, considering the drug's disposition (intravenous administration, short plasma half-life, etc.), indicated minimal effect on the exposure of midazolam (a CYP3A probe) in humans, even at an inhibition potency that is an order of magnitude higher than that obtained *in vitro*. The simulation results obviated the need for the US FDA review team to request a PMR study to evaluate a possible interaction between cabazitaxel and CYP3A substrates in humans.[23]

Case 2—Extrapolation to Unstudied Drug Interaction Scenarios

Fesoterodine is a prodrug of 5-hydroxymethyl tolterodine (5-HMT) for the treatment of overactive bladder. The recommended initial dose is 4 mg daily, which can be increased to 8 mg once daily. The active moiety 5-HMT is significantly metabolized by CYP3A4 and polymorphic CYP2D6, in addition to undergoing renal excretion. Several drug interaction and pharmacogenetic studies have been conducted in CYP2D6 extensive metabolizers (EM) and poor metabolizers (PM).[24,25] The results are summarized in Table 3. On the basis of these data, the labeling indicated that the recommended fesoterodine daily dose should not exceed 4 mg when taken with a potent CYP3A inhibitor, such as ketoconazole, itraconazole, and clarithromycin.[26] However, whether fesoterodine dose needs to be adjusted when coadministered with a moderate CYP3A inhibitor (e.g., fluconazole) in subjects with varying CYP2D6 activities, is the next regulatory question. A PBPK model of 5-HMT was constructed using *in vitro* metabolism and human PK data. The model was verified with the available drug–drug interaction and pharmacogenetic data. As shown in Table 3, the model-simulated fold changes in AUC and C_{max} under various scenarios that have been tested in humans were in close agreement with those observed. Compared with CYP2D6 EM without taking fluconazole, the PBPK simulated fold-changes in the AUC of 5-HMT were 1.3 and 2.6-fold, respectively, when fluconazole was coadministered in CYP2D6 EM and PM, respectively. The model simulated exposure data of 5-HMT in CYP2D6 PMs taking a moderate CYP3A inhibitor, along with known data in CYP2D6 EMs taking fluconazole, provided the needed information for regulatory review and decision making.[27] The current labeling indicated that "there is no clinically relevant effect of moderate CYP3A inhibitors on the pharmacokinetics of fesoterodine."[26]

Table 3. Observed and PBPK-Simulated 5-HMT Exposure Changes, Measured by the AUC Ratio of 5-HMT, in the Presence of Strong and Moderate CYP3A4 Inhibitors in Subjects with CYP2D6 Extensive (EM) or Poor Metabolizer (PM) Status

	AUC Ratio of 5-HMT	
	Observed	Predicted
EM with/without ketoconazole	2.3	1.9
PM with/without ketoconazole	2.5	3.3
PM/EM	2.3	1.6
PM with ketoconazole/EM without ketoconazole	5.7	5.4
EM with/without fluconazole	1.3	1.3
PM with fluconazole/EM without fluconazole	–	2.6

Application to Specific Patient Populations–-Pediatrics

Physiologically based pharmacokinetic models have been developed and applied in pediatric drug development.[28–30] These pediatric PBPK models leverage extensive drug-independent information describing growth- and development-related physiological processes in pediatric patients based on published data.[28–30] Between 2008 and 2012, OCP reviewed six pediatric submissions containing PBPK, four of which were discussed in a recent report describing the application of PBPK in pediatric drug development.[31] The models were used to simulate pharmacokinetics of investigational drugs in pediatric populations of different age groups to support dose selection for clinical trials. For example, a PBPK model of a drug was used to determine the dose for the 12–18-year-old group that would produce systemic exposure levels matching those in adults. On the basis of the clinical

data obtained in this age group, the model was subsequently refined to determine the appropriate doses for younger age groups. Some of these pediatric PBPK simulations also explored situations when a dedicated clinical PK study is difficult to conduct. For example, for a recently approved progestin-containing intrauterine system for prevention of pregnancy,[32] the sponsor used PBPK to simulate plasma exposure of levonorgestrel in postmenarcheal pediatric subjects (up to 18-year old). A physiological uterine compartment was incorporated into the PBPK model, which allowed simulation of uterine drug release using kinetic data determined *in vitro*. The simulated pediatric PK of levonorgestrel in pediatric subjects supported the use of this product in a pediatric trial for females postmenarcheal to 18, an age group for which there is currently no data.

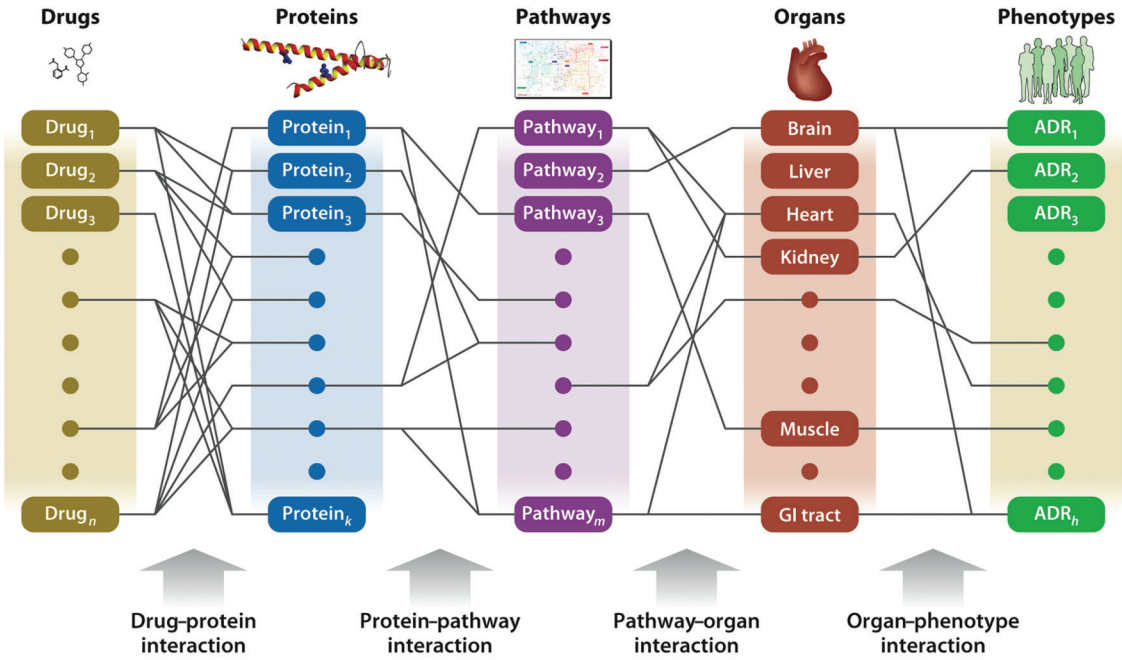
A recent US FDA Clinical Pharmacology Advisory Committee meeting[33] discussed the clinical pharmacology aspects of pediatric clinical trial design and dosing to optimize pediatric drug development. The committee endorsed the use of modeling and simulation in pediatric drug development. Importantly, the committee emphasized that PBPK models need to be prospectively verified using adult PK data, including those from drug interactions, renal impairment, hepatic impairment available at the time of model building.[33] In addition, the committee emphasized the drug's disposition needs to be well defined to yield maximally informative models-based results.

MECHANISM-BASED DRUG SAFETY EVALUATION USING SYSTEMS PHARMACOLOGY

As pharmacology and clinical pharmacology move forward from reductionist approaches toward integrative systems approaches to address problems, OCP has initiated an effort to leverage the new science that is evolving in systems pharmacology.[34] This is focused on the prediction of adverse drug events using the tools of cheminformatics, bioinformatics, and systems biology.[35] To move regulatory science forward in this area, the approach and the tools that still require development have recently been defined.[36]

Ontology of Adverse Events

The initial activities are both within the US FDA and in collaboration with partners in the pharmaceutical industry and academia. The framework for a predictive drug safety systems model is being structured as a series of ontologies at different levels of biological organization.[37] These are developed to organize the massive amount of pertinent information that will populate this framework. (see Fig. 3) This includes an "ontology of adverse events" that is building on



Bai, Jane P.F. and Abernethy, Darrell R., 2013. Annu. Rev. Pharmacol. Toxicol. 53:451–473.

Figure 3. Interaction map showing n number of drugs, k number of proteins, m number of pathways, and h number of adverse drug reactions (ADRs). Abbreviation: GI, gastrointestinal (reproduced with permission from reference D3).

the ontology of adverse events recently developed for characterization of vaccine related adverse events.[38] All of these ontologies are developed in the format consistent with recommendations from the National Centers for Biomedical Ontology to make use of standardized elements in existing ontologies at various levels of biological organization (e.g., gene ontology, cell line ontology, systematized nomenclature of medicine clinical terms).[39] A major challenge that is currently being addressed in this program within the US FDA is the aggregation and definition of MedDRA terms in a manner that allows these terms to be mapped to organ dysfunction, cell dysfunction, and the biological pathways and alterations in gene expression that are associated with drug-induced toxicities. As this evolves, it will constitute the systems pharmacology network that defines a drug mediated adverse event from observed changes in gene expression up through organelle function, cellular expression, organ level toxicity and that ultimately maps to the MedDRA terms.

Databases—Leveraging "Precompetitive" Data

An important element of the program is the collection and organization of drug toxicity data. Published data are relatively easy to obtain and organize, and a number of public and proprietary efforts are creating such databases. These are useful for different forms of data mining and establishing associations between drug toxicities, the data supporting the mechanism of such toxicity, and in some instances the prediction of toxicity from similar chemical structures.[40] In other instances the prediction of clinical toxicities based on the biological pathways that are involved based on data in the public domain for drugs that have similar targets has been used.[41] More challenging to obtain are the data contained in drug development programs, either those that were successful, or equally important, those that were not successful due to drug toxicity or for other reasons. An effort is underway to encourage pharmaceutical companies to define what of these data can be viewed as "precompetitive" and can be shared to build more complete drug toxicity databases that are publicly available. All of these data will be placed in a common platform that allows easy integration across different data formats. A likely platform for this will be tranSMART, a utility developed within the pharmaceutical industry, but recently placed in the public domain under a nonprofit 501c3 format.[42,43] We believe this will evolve into a public drug safety data warehouse that will be modeled after other such data warehouses sponsored by US FDA such as the EKG data warehouse.[44] Going forward such a resource will contain the data necessary to populate the systems networks that are defined for specific drug toxicities and their mechanism. In addition it is likely to be useful to the greater drug development community to allow greater efficiency for drug candidate toxicity prediction and thus drug candidate selection or patient population selection for a drug candidate. At present such databases reside in many of the larger pharmaceutical companies, however they are limited to the data that resides in that company and to some extent augmented by data in the public domain.

Initial Test Cases: Cardiotoxicity and Hepatotoxicity

The extent of the systems network needed to effectively predict particular drug toxicities is likely to be variable depending on the target(s), both desired and not desired, for the drug or series of related drugs to be evaluated. An initial "use" case is being developed to study the non-QT cardiotoxicity of tyrosine kinase inhibitor drugs. The clinical reports of depressed left ventricular cardiac function with exposure to selected tyrosine kinase inhibitors have certainly raised a potential safety signal.[45] However, the extent or reversibility of this cardiotoxicity is not clear and it is also unclear if this is a class effect or only tyrosine kinase inhibitors that target specific kinases are implicated. The predictive systems model for this case is being developed as a collaborative effort, primarily at the Systems Biology Institute [46,47] and the University of Tokyo with the US FDA as a collaborative partner. A number of pharmaceutical companies are expressing interest in joining the collaboration, as there is extensive effort to target various tyrosine kinases for an increasing number of clinical indications.

A systems network for the prediction of drug induced hepatotoxicity is being developed at The Hamner Institute in collaboration with a number of pharmaceutical companies and with US FDA interacting and contributing when appropriate. This is a very highly specified model that encompasses a limited, but very well characterized, systems network. The utility of this approach from *in vitro*/*in vivo* extrapolation and across species hepatotoxic effects for methapyrilene and acetaminophen was demonstrated.[48] This is somewhat in contrast to other systems analysis efforts such as the one at the Systems Biology Institute, which cover a wider systems network, however with relationships between nodes in the system less well characterized. As experience accumulates, the comparative utility of these approaches or a synthesis of them will become more evident. At this time the extent of the overall system and how well characterized the relations between nodes and edges of the system are necessary for a particular predictive drug toxicity problem requires further exploration and testing.

Applications of this program to regulatory decision making has to date been focused on the use of data mining to establish relationships between common biological pathways across drugs and targets and

expected or observed clinical safety signals. In addition the tools of cheminformatics have been incorporated to predict toxicities based on molecular structural elements of the drug or compound class in association with the biological pathways affected. This latter activity is a further evolution of the quantitative structure–activity relationship effort that has been ongoing at US FDA for some years.[49] The outcomes have been incorporation of added safety information in labeling in some cases, providing a basis to not include certain risks in other cases, and signal strengthening and in some cases signal weakening based on pharmacological mechanistic rationale for potential safety signals noted in post market adverse event monitoring.

CONCLUSION AND FUTURE DIRECTIONS

United States Food and Drug Administration has been proactive in the development of regulatory science to address an array of public health challenges. Modeling and simulation have been important scientific investment areas for US FDA's OCP, and will continue to be a major area of growth. Modeling and simulation, tools of quantitative and systems pharmacology, will need to be put into the larger translational science context to reach full potential. Key issues will need to be addressed (probably in a recurring fashion) to see enhanced uptake of modeling and simulation approaches in drug regulation.[50–52] Key needs include:

- Better understanding of the mechanisms of drug action, including off target effects and maximal elucidation of the disposition pathways of drug molecules
- "Vertical integration": synergistic assimilation of the bottom up (cellular level) and the top-down (organism level) models to scale from molecular interactions to organismal physiology
- Targeted training and education of regulatory and nonregulatory scientists
- Sharing of precompetitive data (preclinical and clinical datasets); efficient use of the private–public partnership models to foster academia–industry–government interactions
- Development of best practices in the development of models fit for regulatory use
- Development of mechanisms that allow for timely evaluation (and reevaluation) of models in view of rapidly evolving methodologies and science
- Development of robust PD markers to facilitate the continuing development in the E–R relationship

Despite these challenges, improved understanding of molecular mechanisms is enabling us to employ modeling and simulation in evaluation of "subset" effects (based on subtype of diseases, age, sex, race, genetics, organ dysfunctions, concomitant medications, etc.). For example, recently published US FDA guidance documents related to drug interactions[53] and early phase pharmacogenomic evaluation[54] have included recommendations for the use of PBPK where appropriate. There are several US FDA and ICH guidelines that discuss the relevance of modeling in several aspects of drug development.[51,55,56] Meaningful, pragmatic advice to drug developers will need to be science and experience based. As such, the knowledge gained from predict-learn-confirm exercises will contribute to regulatory decision making, and collaboration among stakeholders—industry, global regulatory agencies, academia, and others will be important.[2,4,6,57,58]

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