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SHORT REPORT

Modeling and simulation for medical product development and evaluation: highlights from the FDA-C-Path-ISOP 2013 workshop

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Abstract Medical-product development has become increasingly challenging and resource-intensive. In 2004, the Food and Drug Administration (FDA) described critical challenges facing medical-product development by establishing the critical path initiative [1]. Priorities identified included the need for improved modeling and simulation tools, further emphasized in FDA's 2011 Strategic Plan for Regulatory Science [Appendix]. In an effort to support and advance model-informed medical-product development (MIMPD), the Critical Path Institute (C-Path) [www.c-path.org], FDA, and International Society of Pharmacometrics [www.go-isop.org] co-sponsored a workshop in Washington, D.C. on September 26, 2013, to examine integrated approaches to developing and applying model-MIMPD. The workshop brought together an international group of scientists from industry, academia, FDA, and the European Medicines Agency to discuss MIMPD strategies and their applications. A commentary on the proceedings of that workshop is presented here.

Keywords Regulatory science · Modeling and simulation · Quantitative drug development · Pre-competitive research · (Q)SAR · Pharmacometrics · Biostatistics

Applying MIMPD in regulatory decision-making—FDA experience

FDA's Center for Drug Evaluation Research (CDER) integrates quantitative tools into the drug-evaluation process from exploratory, preclinical, and clinical stages to regulatory decision-making. Clinical trial simulations (CTS) are used extensively to explore and optimize different trial designs that will address the intended endpoints,

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while traditional pharmacokinetic and pharmacodynamic modeling is used to support drug-approval.

The Division of Applied Regulatory Science at CDER uses (Quantitative) structure–activity-relationship [(Q)SAR] models to predict biological activities such as toxicity from chemical structures [2], particularly when actual safety data are incomplete or unavailable. FDA has included (Q)SAR as part of a Computational Toxicology Consultation Service (Table 1a). Since (Q)SAR modeling does not require synthesis, it allows for more rapid and inexpensive assessments [Appendix].

The Division of Pharmacometrics in CDER's Office of Clinical Pharmacology (OCP) is part of an interdisciplinary team that reviews Investigational New Drug (IND) applications, NDAs, biological licensing applications (BLAs), and QT-studies. Pharmacometric analyses using exposure–response models provide a fundamental understanding of drug effect based on Phase II studies and guide decisions. Modeling has helped in dose-optimization, extrapolation of therapeutic benefit for new drug application (NDA), and to evaluate sub-population efficacy/safety. Analyses to extend learnings beyond those intended in the pre-specified analyses are also performed, which are often used to justify dose-optimization and adjustment. Simulations can also be used to establish dosing recommendations and understand the consequences of missing doses (Table 1b) [Appendix].

The Office of Biostatistics in CDER uses modeling and/or simulation in their regulatory reviews of INDs/NDAs/BLAs to provide regulatory-science recommendations. Review examples across indications for efficacy assessment and other types of studies including bioequivalence carcinogenicity, and safety evaluations were presented (Table 1c). For instance, simulations in confirmatory trials can be performed to evaluate the properties of trial designs and statistical analysis strategies under multiple scenarios with a variety of models assumed [3]. Simulations can also be used to assess the pattern of missing data. The irbesartan-hydrochlorothiazide combination is a statistical modeling example that impacted drug-labeling [Appendix], which becomes part of the labeling requirement of future drug sponsors for a drug class of anti-hypertensives [4, 5].

MIMPD and translational pharmacology—industry perspective

Industry uses modeling to gain knowledge from completed trials and to increase the efficiency of future studies, particularly in supporting the use of biomarkers as medical-product development tools [4, 5]. The Polycystic Kidney Disease (PKD) Outcomes Consortium, a collaboration of Critical Path Institute (C-Path), CDISC, the PKD Foundation, and four academic medical centers (Table 2) recently submitted qualification documents to the FDA and EMA for total kidney volume (TKV) as a prognostic biomarker for PKD clinical trials. This type of model-based enrichment will optimize sample size and study duration, reducing costs and patient exposure to potential toxicities [Appendix]. These quantitative models are drug-independent, but can be customized by introducing compounds and particular biomarkers to demonstrate how the compound changes the biomarker. The biomarker-disease model developed by Pharsight and C-Path simultaneously assessed the trajectory of TKV and the probability of disease outcome in PKD patients (worsening of kidney function and end-stage renal disease). Simulations through the model will support trial enrichment strategies and increase efficiency by optimizing sample size and study duration, potentially reducing costs and patient exposure to potential toxicities [Appendix].

In 2013, FDA and EMA both endorsed for the first time a CTS tool. This drug-disease-trial model developed by the Coalition Against Major Diseases (CAMD) with leadership from Pfizer and Metrum Research Group, included placebo-arm data from Alzheimer's disease (AD) clinical trials. CAMD is one of seven consortia at C-Path, established to advance the goals of the critical path initiative [Appendix]. The process to achieve regulatory endorsement for this CTS tool was lengthy and required a close partnership with regulatory scientists, yet demonstrated the feasibility of working through consortia to deem quantitative tools as "fit-for-purpose" by FDA and "qualified" by EMA, so the whole community can utilize them in confidence (Table 2). Although resource-intensive, the data-management process was fundamental to success. Nonetheless, in the absence of such consortia and a commitment

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Table 1 (a) Center for Drug Evaluation and Research (CDER) Computational Toxicology Consultation Service; (b) case studies for pharmacometrics modeling at FDA; (c) example uses of statistical modeling in exploratory and confirmatory trials

Examples from FDA	
(a) FDA/CDER computational toxicology consultation service	
Examples of applicability	Capabilities offered
Contaminants, degradants, metabolites	(Q)SAR analysis
Interpretation of equivocal toxicology study results	Structure similarity searching ("read across")
Retrospective analysis of post-market safety signals	
(b) Pharmacometrics/Post-hoc learning analysis in key decision-making at FDA	
Ticagrelor (post hoc performed by the sponsor)	Paliperidone
Post-hoc model-based learning analysis contributed significantly to the approval decision and dose recommendation	Unstudied regimen was approved
A model applied to the study data from international sites established a similar ASA dose-efficacy relationship	FDA's alternative strategy and individualized maintenance dose were agreed upon with the sponsor
	PK simulation led to recommendations for dosing window, handling missing doses, switching from prior treatments, and dosing regimen for special patients
	Model-based recommendations are included in the product label
(c) Statistical modeling	
In exploratory trials	In confirmatory trials
Apply informative learning using a variety of models to gain preliminary observation for making go/no-go decisions in adaptive or fixed design contexts	Useful tools to inform among choices of rigorous study designs based on its primary study objectives
Gain useful insight from exploratory studies and to improve the probability of correct selection on design elements based on early phase exploration	Identify optimal statistical testing procedure with multiple endpoints, multiple subgroups of interests, or multiple arms with assumed dose-response model(s) at trial planning
Ability to make go decision using accumulated preliminary knowledge and/or root-cause analysis	Selection of a valid multiple comparison procedure that is robust to dose-ranging model misspecification
Inform dose range, early efficacy, early safety/tolerability, patient population, potential missing data pattern, etc., for later confirmatory trial planning	Convey useful information to consumers and prescribers, especially where there are profound public health impacts, e.g., Avalide drug labeling [4, 5]
Evaluate choices on the number of dose groups to investigate further	Explain relationship between baseline characteristics, e.g., prognostic or predictive baseline factors, and clinical outcome with proper model diagnostics

Table 2 (a) Polycystic Kidney Disease Outcomes Consortium; (b) coalition against major diseases; (c) Metrum Research Group; (d) Escher Project, University Medical Center Groningen

Examples from Consortia/Industry/Contract Research Organizations (CROs)/Academia	
(a) Quantitative tools to support biomarker qualification	
Objective	Approach
Understand total kidney volume (TKV) progression	Mixed-effects model for TKV change as a function of time
Understand time-changing probabilities for clinically-relevant endpoints	Time-to-event model using relevant covariates
Join the two previous to link the longitudinal outcome to the hazard	Joint model to quantitatively link the longitudinal outcome to the hazard
(b) Clinical trial simulation tool for mild and moderate Alzheimer's dementia	
Description of the tool	Underlying structure
A clinical trial simulation tool to help optimize clinical trial design for mild and moderate AD, using the Alzheimer's Disease Assessment Scale (Cognitive Subscale) (ADAScog) as the primary cognitive endpoint	A drug-disease-trial model that describes disease progression, drug effects, dropout rates, placebo effect, and relevant sources of variability
Regulatory endorsement from FDA	Regulatory endorsement from EMA
Deemed "Fit-for-purpose" for: Sample size Determination of optimal trial durations and treatment effect measurement times Comparison of the sensitivity of competing trial designs to assumptions about the types of expected treatment effects (time to maximal effect, effects that increase or decrease over time) Determination of the most appropriate data analytic methods for novel trial designs	Suitable for qualification for use in medical-product development as a longitudinal model for describing changes in cognition in patients with mild and moderate AD, and for use in assisting in trial designs in mild and moderate AD, as defined by the context of use
(c) Quantitative model of the joint progression of multiple endpoints in pre-dementia in Alzheimer's disease	
Insights from psychometrics	Advantages of modeling progression as a latent variable
Correlation between multiple items that measure the same unobservable trait	Disease-modifying effects could be defined as a % change in time of natural progression relative to a particular disease endpoint, rather than a % reduction in score on a particular cognitive instrument
Such correlated items can be integrated into one instrument (rather than quantifying them in isolation)	Increased precision in inference of individual endpoints (if a valid model structure is present)
Lack of correlation between groups of items may suggest more than one underlying trait	Increased understanding of correlations, with more informative measures of potential causal relationships, and the extent to which a biomarker might be useful as a surrogate endpoint
	Increased understanding of the operating characteristics of novel composite endpoints

Table 2 continued

(d) Escher Project, University Medical Center Groningen: Using multiple biomarkers to predict renal and cardiovascular drug efficacy	
The challenges	The multiple parameter risk response efficacy (PRE) score
Antihypertensive drugs that intervene in the Renin-Angiotensin-Aldosterone-System (RAAS) have many more short-term (off-target) effects than the on-target effect of blood pressure lowering These off-target effects include changes that contribute either in a positive or negative way on final CV/renal outcome	Combining the off-target short-term effects into a multiple parameter risk response efficacy (PRE) score might give better prediction of final long-term renal and cardiovascular outcome Potential advantages for Phase IIb/Phase III: Better prediction of the potential results of drugs on CV/renal Aid in selection optimal dose for phase III trials Aid in clinical trial design

to data sharing, companies will continue in isolation to develop models that will be unavailable to others in the field [Appendix], and that may not meet regulatory endorsement.

To develop a comprehensive quantitative understanding of pre-dementia stages in AD, Metrum Research Group is developing innovative approaches, which consider disease progression as a latent variable and allow for the incorporation of multiple biomarkers and other factors (Table 2). In the cardiovascular field, the Escher project and the University Medical Center Groningen have developed a modeling approach to integrate on-target and off-target effects of antihypertensives into a multiple parameter risk response efficacy (PRE) score, which might provide improved predictions of long-term renal and cardiovascular outcomes (Table 2) [Appendix]. The group is now partnering with the pharmaceutical industry, EMA, FDA, and C-Path to apply the PRE score in medical-product development and regulation [6].

Future perspective for MIMPD

Given the value of MIMPD to regulators and industry, innovation in the field can be expected in the coming years, including translational models and CTS tools for combination medical-product development and collaborative approaches to mechanistic modeling that provide improved predictive accuracy. These approaches apply across an array of disease areas.

For example, the critical path to TB drug regimens (CPTR), another C-Path consortium, in partnership with other non-profit foundations, research organizations, academic institutions, the pharmaceutical industry, and government and regulatory agencies, is applying various modeling approaches to the challenge of tuberculosis (TB) drug-development. These models include the Hollow-Fiber TB in vitro PK/PD platform [7], Monte Carlo simulations of clinical data [8], models that capture the immune response [9, 10], and PK/PD models in circular/proliferative systems [11] (Table 3a, b). Another pre-competitive public–private partnership, the DILI-sim Initiative, led by The Hamner Institutes for Health Sciences, is developing a predictive, mathematical model of drug-induced liver injury (Table 3c) [Appendix].

Making models publicly available to inform regulatory decision-making processes has been recognized as an important priority by the FDA (Table 3d). In addition to many of the types of models already mentioned, the FDA's Center for Devices and Radiologic Health (CDRH) is advancing modeling and simulation tools for medical-device development, which include digital patients and virtual clinical trials, along with establishing a framework for assessing model credibility and ensuring outcomes meet regulatory standards. They have also promoted the FDA

Table 3 (a) CPTR/University of Texas Southwestern Medical Center; (b) CPTR/Leiden experts in advanced pharmacokinetics and pharmacodynamics (LAP&P); (c) The Hammer-University of North Carolina Institute of Drug Safety Sciences; (d) FDA/Center for Devices and Radiological Health (CDRH); (e) Metrum Research Group

Case studies of future quantitative tool development	
(a) In vitro hollow-fiber TB platform: Inform the design of targeted clinical trial in terms of doses used, proportion of patents likely to respond, resistance emergence etc.	
Utility	Clinical application
Examination of drugs in combination at different doses for a synergy plot; rank the regimens or compare to the current standard of care	Prediction of the drug concentrations in humans that will yield optimal outcome
Application of results in modeling and simulation (M&S) to select optimal doses for combination therapy	Prediction of % of patients who will achieve efficacy and % who will develop drug resistance
(b) Gap identification as a critical step to enable integrated clinical trial simulation platforms in tuberculosis (TB)	
Gaps	Proposed solutions
Currently only one common clinical biomarker (colony forming unit—CFU—sputum count or time to positivity—TTP) can be related to a model variable (bacterial load)	Consider appropriate parts of the system biology models and simplifying them by 'lumping' states
CFU/TTP data alone appear not informative enough to characterize all clinically relevant disease trajectories for CTS	Consider options for remapping and rescaling of 'General infectious proliferation model' to TB
Accuracy and precision of model parameter values are not clear (e.g., no sensitivity analysis and no correlations available)	Connect to multiple clinical biomarkers, responding on various time scales, to inform model
(c) DILIsym®	
Preclinical	Clinical
In vitro–in vivo extrapolation (IVIVE)	Drug-induced liver injury (DILI) dose response estimation
Risk-based compound ranking	Variability response prediction
Inform design of preclinical biomarker studies	Clinical biomarker analysis
(d) Making models publicly available: successes and challenges	
Objectives of credible practice of M&S in healthcare	Credibility milestones
Unify M&S vocabulary and terminology	Clear definition of model type
Develop guidelines and "credibility principles"	Thorough description of model development process
Define and demonstrate translational workflows	Clear definition of domains of validity or invalidity
Promote "good practice" through outreach	Enable reproducibility: provide the references for input data/Provide data for cross-validation
Establish model certification process	Regulatory review of meta-data for accurate and appropriate use
(e) Experiences with open and commercial sharing of models, data and modeling tools	
The challenges	Potential solutions
Industry is unwilling to share intellectual property (IP) without assurance they will receive something of value in return	Build on prior successes of Public–Private-Partnerships (PPPs) and Consortia (C-Path, IMI, etc.)

Table 3 continued

(e) Experiences with open and commercial sharing of models, data and modeling tools

The challenges	Potential solutions
Prior agreements with third parties may restrict IP sharing	Prospectively build an infrastructure that allows non-competitive data sharing
Near-term objectives often trump longer term goals addressed by model and data sharing	Build contributed time to Public Private Partnerships (PPPs) and Consortia into full-time employees (FTEs) duties (CAMD, Polycystic Kidney Disease (PKD-OC), and other success stories)
Sharing only model-based tools (without details about the model or the data upon which it is based) limits credibility and further model development as new evidence becomes available	METAMODL and FDA pharmacometrics websites

Digital Library, a mechanism for curating a public open-use repository for models and simulations in non-competitive space [Appendix]. Other approaches to sharing models and data have been developed in the private sector. For example, METAMODL is a web-based library of models, public source outcome data, and software tools managed by the Metrum Research Group (Table 3e) [Appendix] [12].

Discussion

Although MIMPD has made a substantial impact as a supportive tool, this approach has still not become the centerpiece of medical-product development. MIMPD affords robustness in regulatory and development decision-making (dosing, trial design), and enables the development of integrated comprehensive data packages for regulatory submission. Well-developed examples of these approaches are pharmacometric model-based approaches including drug/disease, benefit-risk profiles, and PK/PD. However, integration has lagged in aspects of CTS. While there are examples of successful modeling at the clinical end, the interface with preclinical models could be improved, as exemplified by the work in assessing the risk of proarrhythmia [Appendix]. Phase-dependent modeling from systems to epidemiology was discussed as a potentially valid strategy for medical devices.

The FDA and EMA have played an important role as partners with industry in advancing MIMPD, although currently they act primarily as reviewers. There was a call to engage regulators earlier as intellectual partners in model development. Communication with regulators about models, assumptions, and the evidence needed to demonstrate model credibility throughout the iterative process of MIMPD could reduce the pressure on regulators to review submissions is short amounts of time.

Teams of clinicians, biologists, statisticians, experimentalists, and quantitative scientists can establish a common language and understanding of MIMPD, and clarify the assumptions used in model building. Educational efforts are needed so that modeling approaches become not only acceptable, but desirable and necessary to advance the understanding of disease states and pharmacological responses. Since prescribers and patients are the end stakeholders of products developed through MIMPD, all stakeholders need to disseminate the applications of MIMPD and the necessity for sharing scientific data to support model development and refinement.

Appendix

A1. FDA's plan to advance regulatory science: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM268225.pdf.

A2. Further information on the workshop (including slide presentations): http://c-path.org/modeling-and-simulation-for-medical-product-development-and-evaluation-workshop/.

A3. FDA-approved irbesartan-hydrochlorothiazide combination label (see Figs. 1a, b, 2a, 2b): http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020758s064lbl.pdf.

A4. Coalition against major diseases: http://c-path.org/programs/camd/.

A5. Regulatory decision from FDA on the CAMD AD CTS tool: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180485.htm.

Regulatory decision from EMA on the CAMD AD CTS tool: http://www.google.com/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=1&ved=0CCoQFjAA&url=http%3A%2F%2Fwww.ema.europa.eu%2Fema%2Fpages%2Fincludes%2Fdocument%2Fopen_document.jsp%3FwebContentId%3DWC500146179&ei=zB7LUvG3GMrA2QXkrIHICw&usg=AFQjCNGDBQWSJJX5DjqHc-CFZaArfDeReg&sig2=G9ZUieb3VLs-I8lvTI279g.

AlzForum feature on the regulatory decisions for the CAMD AD CTS tool: http://www.alzforum.org/news/research-news/ad-trial-simulation-tool-receives-regulators-blessings.

Wall Street Journal features on the use of simulations to improve drug development: http://online.wsj.com/news/articles/SB10001424052702303914304579192033377938714. http://online.wsj.com/news/articles/SB10001424052702304361604579290572010514840.

Further audiovisual materials on modeling and simulation (for clinicians and non-modelers): http://c-path.org/category/videos/.

A6. Public Meeting—FDA/NIH/NSF Workshop on Computer Models and Validation for Medical Devices, June 11–12, 2013: http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm346375.htm.

A7. Metamodl: http://www.metamodl.com/index.php?/page/metamodl.html.

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