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Editorial

Editorial on the FDA Report on "*Successes and Opportunities in Modeling & Simulation for FDA*"

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Modeling and simulation (M&S) serve as powerful tools at the United States Food and Drug Administration (US FDA) to support regulatory and scientific efforts, including premarket and postmarket product assessments as well as policy development and implementation for drugs, medical devices, food substances, and tobacco products. In 2016, the Office of the Chief Scientist, FDA, approved the formation of the Modeling and Simulation Working Group (ModSimWG) to encourage the application of M&S data in scientific research and regulatory decision-making and to foster cross-center collaborations across the Agency on M&S-related regulatory science initiatives.[10,17] Recently, the ModSimWG published a report on the successes and opportunities for M&S at the FDA.[10] The report included a broad overview of the different types of M&S approaches used across FDA. Furthermore, it presented a selection of case studies that demonstrate the successful and widespread application of M&S for premarket review, postmarket assessment, policy development, and policy implementation in different FDA Centers. It also highlighted opportunities to further expand the utility of M&S by adopting advanced data analytics and model-based technologies to support FDA's mission to protect, promote, and advance public health.

Figure 1, adopted from Reference 10, presents an overview of the various M&S approaches used at the different FDA Centers to support the Agency's scientific efforts and regulatory assessments. The Center for Drug Evaluation and Research (CDER) applies M&S for quantitative structure–activity relationship ((Q)SAR)-based predictive modeling, assessment of the risks of drug abuse on public safety, and evaluation of advanced technologies to improve drug manufacturing, quality, and availability[4,5,19,21] (Kruhlak 2012). The Center for Devices and Radiological Health (CDRH) reviews M&S results submitted in support of medical device safety and effectiveness, and M&S algorithms implemented in medical device software.[8,18] The Center for Food Safety and Applied Nutrition (CFSAN) utilizes several M&S approaches, including toxicity and toxicokinetic prediction models, exposure assessment models, dose–response models, and illness attribution models to support premarket review, postmarket assessment, policy development and implementation, and to ensure food safety.[10,14–16] In addition to the above-listed applications for premarket review and postmarket assessment, the Center for Biologics Evaluation and Research (CBER) has explored the utility of M&S to perform risk assessments and advance its various research programs, including estimation of the geographical risk of exposure to infectious diseases[26] and development of the Complex Innovative Trial Design (CID) Pilot Meeting Program, in collaboration with CDER, to facilitate the use of CID approaches in late-stage drug development and promote innovation in clinical trial designs for medical products.[12] The Center for Tobacco Products (CTP) developed a multi-state dynamical systems population structure model to evaluate the risks associated with a variety of tobacco product use behaviors on population health and inform policies related to product switching or dual use.[1,22] The Center for Veterinary Medicine (CVM) has applied M&S approaches, such as physiologically-based pharmacokinetic (PBPK) models, in its research and regulatory evaluations to understand the impact of veterinary drugs and formulations on dose/exposure and response relationships.[10] The National Center for Toxicological Research (NCTR) utilizes M&S to address scientific research needs of other FDA Centers that are important to address regulatory science matters, particularly those related to postmarket assessments.[10,20,23–25]

M&S has been successfully used to meet specific goals of scientific research projects and regulatory assessments at FDA. Fourteen case studies on successes of M&S at FDA are presented in Reference 10; a selection of these is briefly discussed here. Recently, CDER developed an investigational Public Health Assessment via Structural Evaluation (PHASE) approach[5] to assess the risks posed by newly identified drugs of abuse, including synthetic opioids on the street-drug market, and provide critical information to law enforcement and the public on emerging illicit opioids. CDRH collaborated in the development of the 'Virtual Family' (VF), a set of four detailed anatomically correct virtual whole-body models of an adult male, adult female, and two children, used to assess

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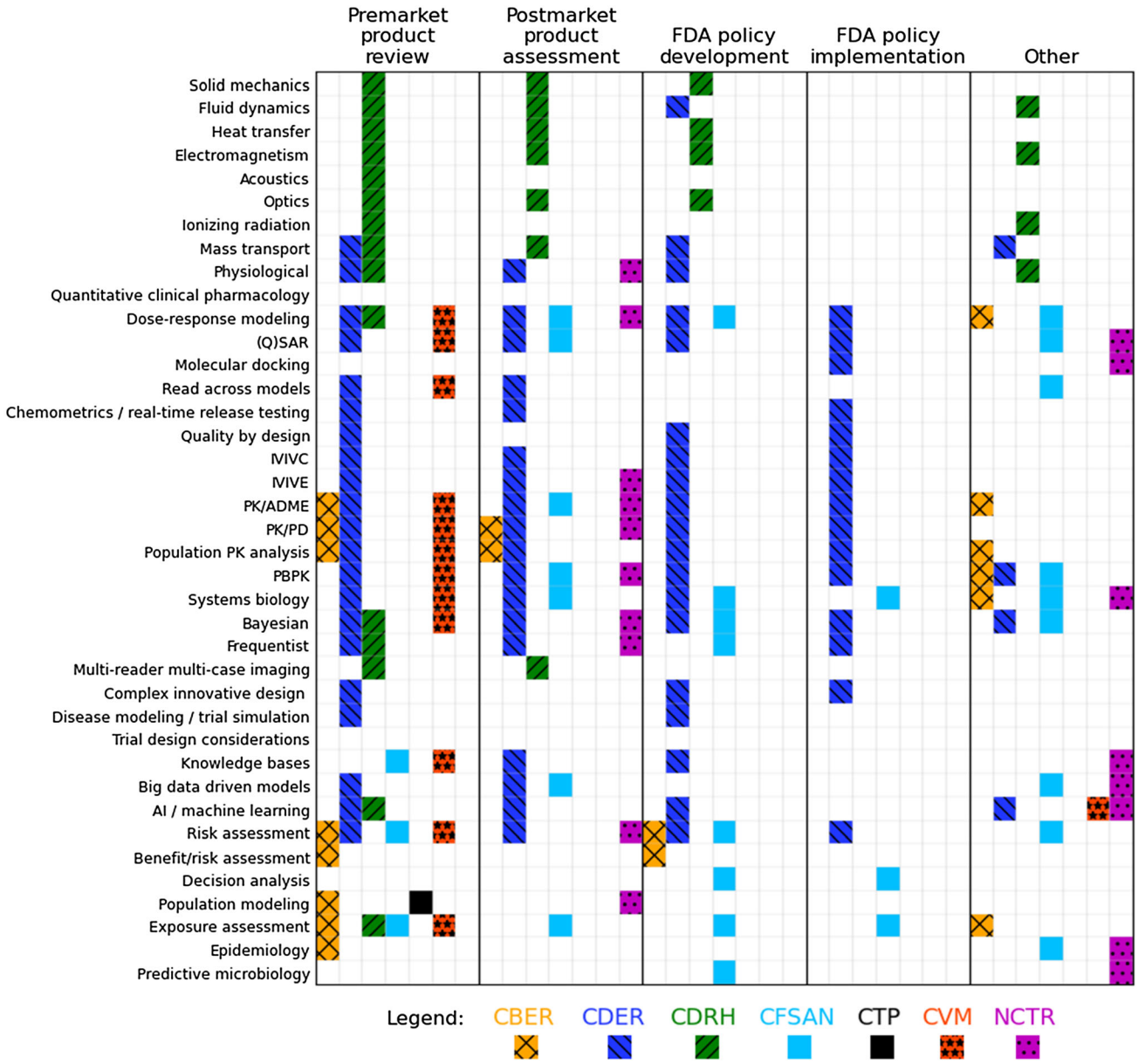

FIGURE 1. Overview of the use of modeling and simulation across FDA, organized by modeling discipline (rows), application area (outer columns) and FDA Center (inner columns, colors). CBER, CDER, CDRH, CFSAN, CTP, and CVM are regulatory product Centers and NCTR is a non-regulatory Center providing regulatory research support to product Centers. *CBER* Center for Biologics Evaluation and Research, *CDER* Center for Drug Evaluation and Research, *CDRH* Center for Devices and Radiological Health, *CFSAN* Center for Food Safety and Applied Nutrition, *CTP* Center for Tobacco Products, *CVM* Center for Veterinary Medicine, *NCTR* National Center for Toxicological Research, *(Q)SAR* (quantitative) structure activity relationship, *IVIVC/IVIVE* in vitro in vivo correlation/extrapolation, *PK* pharmacokinetics, *ADME* absorption, distribution, metabolism, excretion, *PK/PD* pharmacokinetics/pharmacodynamics, *PBPK* physiologically-based pharmacokinetic, *AI* artificial intelligence. Empty spaces should be interpreted as no information collected to date, rather than the absence of work in the area. (Figure adopted from the report on Successes and Opportunities in Modeling & Simulation for FDA[10]).

safety of metallic implants during magnetic resonance imaging.[3] The VF was later expanded into the 'Virtual Population' (VP). Both VF and VP have been widely cited in device regulatory submissions and have contributed to a more effective, predictable, and comprehensive regulatory process.[10] In collaboration with stakeholders from across the medical device industry, CDRH contributed to the development of the American Society of Mechanical Engineers (ASME) Verification & Validation 40 (V&V40) 2018 Standard, the first consensus standard for assessing the credibility of computational models for medical devices. The V&V40 Standard[2] provides a risk-based framework for verification, validation, and quantifying uncer-

tainty in computational modeling of medical devices. Application of the V&V40 Standard to other healthcare products is currently being explored.[13] As a collaborative effort between CFSAN and NCTR, M&S approaches of PBPK modeling and probabilistic exposure modeling were used to contribute to a comprehensive safety assessment of bisphenol-A (BPA).[6] BPA has been used in the production of food contact materials such as polycarbonate beverage bottles and metal can coatings since the 1960s. The models predicted internal exposure levels of BPA and some of its metabolites in infants, children, and adults. Taking into account these internal exposure levels together with the available toxicity data at the time on BPA, FDA concluded that BPA is safe for the currently authorized food-contact uses in food packaging materials.[7]

On January 11, 2021, FDA published the Focus Areas of Regulatory Science (FARS) report[9] that identified data and innovation that rely on M&S as two of the strategic initiatives that would support FDA's mission to protect, promote, and advance public health. As discussed in the FARS report, M&S has substantial potential to facilitate development of FDA-regulated products, support regulatory decision-making and policy development. M&S can be used to predict review timelines for product submissions to FDA, optimize regulatory and research workload, and enhance resource allocation. Integrating M&S approaches such as mechanistic- or physics-based models with statistical- or machine-learning-based models would enable FDA to evaluate data from multiple sources, build enhanced data visualization capabilities, identify current data gaps, and harness the full potential of M&S to solve critical problems. Development of guidelines for good simulation and modeling practices will promote harmonization across the Centers within FDA and across international regulatory bodies, as applicable.

In conclusion, M&S has widespread application in promoting the development of innovative research tools and regulated products at FDA. Model-informed product development can be used to predict potential product safety issues and clinical outcomes, optimize drug dosing/therapeutic individualization and product performance, and evaluate mechanisms of potential adverse events associated with any FDA regulated products.[9,11] M&S can inform the establishment of scientific standards to ensure therapeutic equivalence in patients.[9,11] FDA has committed resources to transform computational modeling from a valuable scientific tool to a valuable medical device regulatory tool.[9,11] This focus on employing M&S to support product innovation and development of novel life-saving technologies coincides with the explosive growth in data science and model-based technologies across industry to advance public health. Alternative methods and emerging techniques that integrate modeling across different disciplines and incorporate data from multiple sources will strengthen FDA's M&S capabilities and improve its engagement with the stakeholders.

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