U.S. FOOD & DRUG ADMINISTRATION





Successes and Opportunities in Modeling & Simulation for FDA

A Report Prepared by the Modeling & Simulation Working Group of the Senior Science Council

Contents

Main contributors

Kausar Riaz Ahmed (CDRH)*
Pras Pathmanathan (CDRH)*
Shruti V. Kabadi (CFSAN)
Jane Van Doren (CFSAN)
Naomi Kruhlak (CDER)
Annie Lumen (formerly NCTR)
Marilyn Martinez (CVM)
Tina Morrison (OC/OCS)
Paul Schuette (CDER)
Million Tegenge (CBER)

Other contributors

Jason Aungst (CFSAN)
Omari Bandele (CFSAN)
Yuhuan Chen (CFSAN)
Brent Craven (CDRH)
Sherri Dennis (CFSAN)
Mary Ditto (CFSAN)
Christopher Ellis (CDER)
Wendy Fanaselle (retired, CFSAN)
Jeffrey Fisher (retired, NCTR)
Prasanna Hariharan (CDRH)
Huixiao Hong (NCTR)
Wolfgang Kainz (retired, CDRH)
Colleen Kuemmel (formerly CDER)
Yitong Liu (CFSAN)
Antonia Mattia (retired, CFSAN)
Edwin Matthews (retired, CFSAN)
David Oryang (CFSAN)
Hao Pang (CFSAN)
Antonio Paredes (CTP)
Paulina Rodriguez (CDRH)
Sugunadevi Sakkiah (formerly NCTR)
Geng Tian (CDER)
Rajeshwar Verma (CFSAN)
Patra Volarath (formerly CFSAN, now CDER)
Xiaoming Xu (CDER)
Hong Yang (CBER)

*Corresponding authors: **Kausar.RiazAhmed@fda.hhs.gov**, **Pras.Pathmanathan@fda.hhs.gov**

Feedback

We welcome questions, comments, or other feedback. Please email the corresponding authors or **OC-OCS-WG-Modeling-Simulation-Leadership@FDA.onmicrosoft.com** with "FDA M&S Report" in the subject line.

Introduction

Computational (*in silico*) modeling and simulation (M&S) are powerful tools that complement traditional methods for gathering evidence – including bench-top (*in vitro*) testing, and animal or clinical (*in vivo*) studies - about products regulated by the Food and Drug Administration (FDA) or for developing FDA policy. FDA scientists routinely review results from M&S studies submitted by industry and use M&S approaches for scientific research and regulatory decision-making. In the last decade, M&S has become firmly established as a regulatory science priority at FDA, which has coincided with the explosive growth in data science and model-based technologies.

In 2016, FDA's Office of the Chief Scientist approved the formation of the Modeling and Simulation Working Group (ModSimWG). Made up of nearly 200 FDA scientists, the ModSimWG brought together M&S scientists across the Agency to:

- raise awareness about the types and uses of M&S at the FDA;
- support the implementation of M&S in the regulatory review process across the FDA;
- develop mechanisms for establishing the credibility principles for M&S used for research and regulatory decision-making;
- serve as a scientific advocacy and an advisory platform for M&S issues relevant to FDA's mission and objectives;
- provide input on reporting and strategic planning for M&S topics affecting regulatory science;
- serve as a liaison to the Scientific Computing Board (SCB) and other Agency groups on scientific issues regarding M&S; and
- discuss diverse issues related to M&S, share ideas and information, and collaborate.

The ModSimWG is organized across six Interest Groups, with a Leadership Circle comprising two representatives from each FDA Center (including all six product Centers and the National Center for Toxicological Research (NCTR)) and one representative from the Office of Regulatory Affairs (ORA).

While the importance and potential of M&S is acknowledged by FDA leadership, the Working Group identified that there was limited information, both internally and externally, on how M&S is used across and within FDA Centers, and the impact it has had on FDA's mission to protect public health. To address this knowledge gap, the Working Group developed this report, which, describes the role and impact of M&S across the Agency.

There are three main aims of this report: first, to elucidate how and where M&S is used across FDA, and the type and purpose of M&S used; second, to present a selection of M&S case studies from across the Centers, which demonstrate how M&S is playing a tangible role in FDA fulfilling its mission; and third, to identify opportunities for FDA to better harness M&S in upcoming years by embracing computational advances and new (and big) data streams to develop improved public health solutions.

Modeling and Simulation at FDA

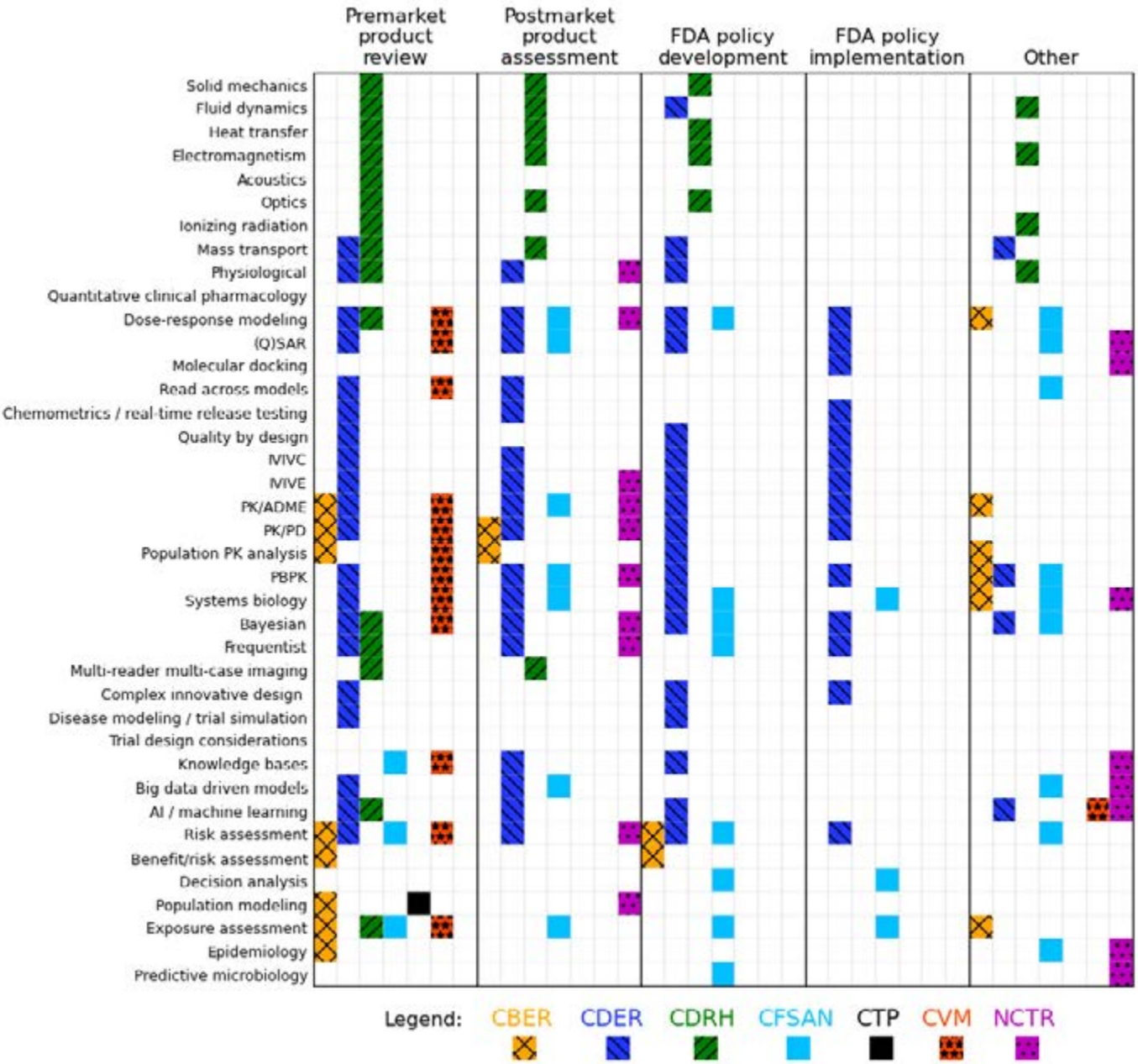
To assess the status of regulatory applications of M&S at FDA and develop a better understanding of how M&S is used across the Agency, FDA scientists were surveyed on how M&S tools are relevant to their work. Results were organized by the relevant FDA Center, modeling discipline, and application area as it pertains to FDA's regulatory roles. For the latter, the following categories were used:

- *Premarket product review*: M&S is used during the premarket review of a Center-regulated product, e.g., sponsor submitting M&S evidence for FDA to review, or FDA scientists using M&S for premarket regulatory science;
- *Postmarket product assessment*: M&S is used in postmarket assessment of a Center-regulated product, e.g., in root cause analyses;
- *Policy development*: M&S is used by FDA for policy development, e.g., identifying where interventions or mitigations could reduce consumer risk and quantitatively evaluating the public health impact of proposed rules or guidance;
- *Policy implementation*: M&S is used by FDA for policy implementation, e.g., prioritizing resource allocation using data-driven, risk-based decision analysis models;
- *Other:* anything that did not fall in the above categories; some examples below.

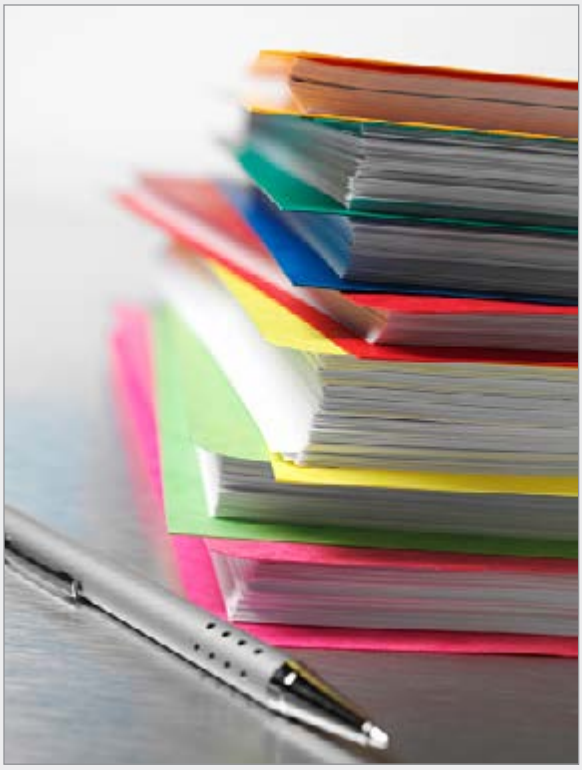
The survey was first performed in 2019 and updated in 2021. Figure 1 shows an overview of the results.

The results illustrate the widespread use of M&S at the Center for Drug Evaluation and Research (CDER), where it is used in premarket and postmarket product applications and in policy development and implementation. The Center for Devices and Radiological Health (CDRH), the Center for Food Safety and Applied Nutrition (CFSAN), Center for Biologics Evaluation and Research (CBER) and the National Center for Toxicological Research (NCTR) also report significant use of M&S. At CDRH, M&S is most relevant to product premarket review or postmarket assessment, although the 'Other' category includes cases where a computational model *is* the medical device. The figure reveals that there is currently very little overlap between modeling disciplines used at CDRH and the other Centers. At CFSAN, M&S is used for premarket review, postmarket assessment, policy development and implementation, and 'Other' modeling efforts that support these efforts, such as illness attribution models, dose-response models, human toxicity prediction models, exposure assessment models, and creation of modeling frameworks/platforms. CBER employs M&S for premarket and postmarket review and policy development and is also exploring the appropriate application of M&S through various research programs (Other). NCTR uses M&S to support postmarket assessment in collaboration with the FDA product Centers and the 'Other' category primarily focuses on development of a variety of *de novo* M&S tools to better position the FDA to respond to its regulatory science needs with emerging technologies. The Center for Tobacco Products (CTP) and the Center for Veterinary Medicine (CVM) also reported use of M&S. CTP reported using population-based modeling approaches for premarket review. CVM is in its early stages of applying M&S to its regulatory evaluations. Currently, it is being applied primarily to increase an understanding of the impact of veterinary drugs and formulations on dose/exposure relationships (e.g., physiologically-based pharmacokinetic models). In terms of pre-approval applications, M&S is a component of risk and exposure assessments, systems biology, and read-across models (see Figure 1). The application of M&S is expected to increase significantly in future years, across all Centers. Potential opportunities are discussed in the final section of this report.

Figure 1: *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.* **Acronyms:** *(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 yet, rather than no work done in the area.** *Different Centers may have different interpretations of some of the modeling disciplines.*



Case Studies



The second aim of the report is to demonstrate how M&S is already playing a vital role in supporting FDA's mission. In this section, a series of case studies are presented to illustrate how M&S has been used by FDA scientists to protect and advance public health. These case studies represent only a sample of successful M&S projects across FDA; many other case studies could have been included.

The case studies presented below cover nearly all Centers across the Agency, and illustrate use of M&S for premarket product review, postmarket assessment, and policy development or implementation. Several involve the use of M&S to answer specific regulatory questions. Others describe development of resources for FDA scientists or for the scientific community. Yet others describe programmatic efforts around M&S.

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Public Health Assessment via Structural Evaluation (PHASE): a structure-based approach for assessing the risk a new drug of abuse poses to public safety

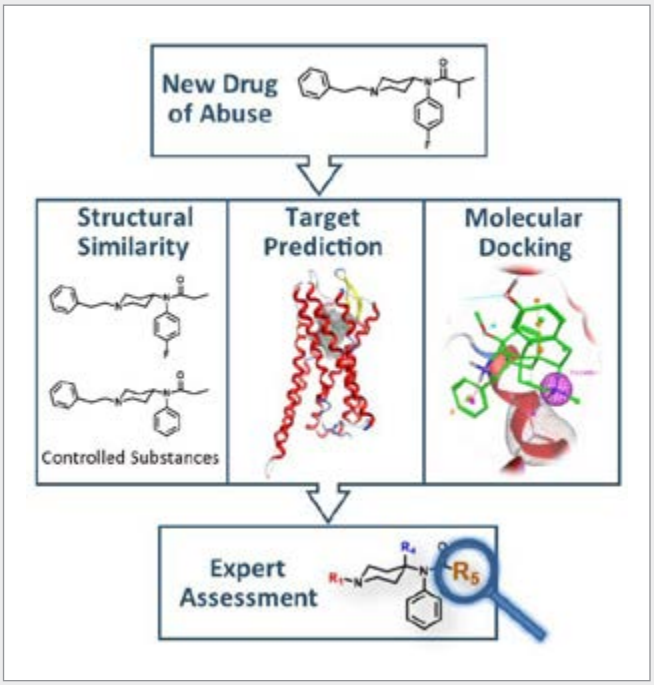
Executive summary

CDER developed the Public Health Assessment via Structural Evaluation (PHASE) *in silico* methodology to provide a structure-based evaluation of a newly identified opioid's risk to public safety. PHASE utilizes molecular structure to predict biological function. The multi-component computational approach coupled with expert review provides a rapid, systematic evaluation of a new drug in the absence of *in vitro* or *in vivo* data. The information provided by PHASE can inform law enforcement agencies and the public with vital information regarding newly emerging illicit opioids.

New synthetic opioids have become a significant threat to public safety. In particular, the emergence of new fentanyl derivatives on the street-drug market has led to a rapid increase in overdose deaths. The large influx of new fentanyl derivatives is attributed to their high potency and inexpensive synthesis. Unfortunately, there are often little to no pharmacological and toxicological data available and the resource requirements to experimentally evaluate all possible fentanyl analogs are prohibitively high. As such, a computational risk-assessment model is desirable.

Therefore, CDER developed PHASE, a multi-component computational strategy for evaluating the risk that new opioids pose to public safety. PHASE is comprised of four components that calculate a new drug's structural similarity to all previously scheduled drugs, identify plausible biological targets with target prediction software, predict binding affinity at the mu opioid receptor with a molecular docking simulation, and integrate experimental and predicted data to generate an overall conclusion [1-2].

PHASE can be used to prioritize experimental inquiry into the potential effects of newly identified drugs of abuse and assist with emergency scheduling. Additionally, it was used to provide supporting evidence of the opioid properties of kratom, an unapproved botanical substance. The results of the assessment were featured in a 2018 statement released by then FDA Commissioner, Dr. Scott Gottlieb [3].



Modeling and simulation-guided postmarket assessment of bisphenol-A (BPA)

Executive summary

In response to potential public health concerns, the FDA conducted a comprehensive food safety assessment involving physiologically-based pharmacokinetic (PBPK) modeling and probabilistic exposure modeling to conclude that bisphenol-A (BPA) is safe for the currently authorized food-contact uses in food packaging materials [4]. This assessment is a collaborative effort between CFSAN, NCTR, and an Agency level working group under the Office of the Chief Scientist.

Bisphenol-A (BPA) has been used in food packaging since the 1960s as a component of food contact materials, such as polycarbonate beverage bottles and metal can coatings, to protect food from contacting metal surfaces. As a result, humans have been widely exposed to BPA. Reports of reproductive and developmental BPA toxicity in laboratory animal studies raised safety concerns regarding the food-contact uses of BPA [5]. However, the health concerns from exposure to BPA, in part, stemmed from disparate and contradictory reporting on health outcomes and from compromised analytical measurements (e.g., contamination issues) for BPA and metabolites in biological samples. The National Toxicology Program (NTP) partnered with NCTR to carry out in-depth toxicity testing and pharmacokinetic studies on BPA and its metabolites [6-12].

The experimental data gathered was used to support the development of a mechanistically-informed PBPK model for BPA [12-14]. This model predicted that the peak serum levels of BPA were orders of magnitude below estrogen receptor affinities (picomolar concentrations), the receptors hypothesized to be responsible for previously reported effects. The PBPK model findings also indicated that an uncertainty factor of less than 10 would be acceptable to account for inter-individual variability in the PK of BPA, highlighting the impact of mechanistic modeling and simulation in risk assessment. In addition to the toxicological evaluations, CFSAN performed a more refined exposure assessment utilizing a probabilistic modeling approach to analyze both in-house and published data on BPA concentrations in formula (as a result of formula reconstitution in polycarbonate bottles) and BPA concentrations in toddler and adult food [15]. The new modeling approach resulted in exposure estimates that were less variable for infants (0 to 12 months of age) and more precise for children and adults (>2 years of age) when compared to the previous deterministic approach.

The results of the probabilistic exposure analysis were paired with toxicological assessment based on predictions of the PBPK model to conduct a thorough safety evaluation of BPA [16], which ultimately supported FDA's regulatory assessment of BPA. This regulatory research project highlights the utility of exposure-based and mechanistic modeling for characterizing the exposure levels of BPA and the associated risk to humans by predicting the internal exposure levels for BPA and its metabolites, examining age and species differences in pharmacokinetics, and addressing inter-individual variabilities in a population.

Predicting the safety of drug impurities using (quantitative) structure-activity relationship models

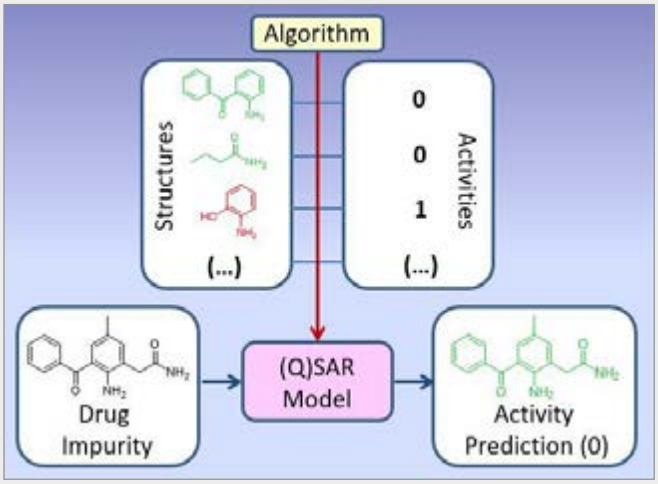
Executive summary

(Quantitative) structure-activity relationship, or (Q)SAR, models make computational predictions of toxicity for a molecule based on chemical structure. FDA's CDER established a comprehensive research program to develop databases and (Q)SAR models to predict the genetic toxicity of molecules in pharmaceutical applications when standard test data are limited or unavailable. This work culminated in the 2014 publication of a globally harmonized regulatory guidance that recommends the use of (Q)SAR models for assessing the genetic toxicity of drug impurities. CDER continues to lead an active regulatory research program in this area by enhancing models used for regulatory purposes, defining best practices for model application, and communicating regulatory expectations for submissions to external stakeholders.

In the late 2000s, CDER invested significant resources into developing manually-curated databases of toxicology results linked to chemical structures [17]. These databases were then used to develop computational (Q)SAR models that identified associations between chemical structure and biological activity, such as genetic toxicity. The resulting models were used to fill data gaps when standard toxicology studies were unavailable for molecules in pharmaceutical applications [18].

Drug impurities emerged as a strong use-case for this methodology [19]. Pharmaceuticals have the potential to include hundreds of impurities at varying levels and pharmaceutical companies need to determine whether these impurities pose a significant risk to human health. (Q)SAR models predict with high sensitivity the likelihood that an impurity will be a mutagen. They also provide the high- throughput capacity needed to assess large numbers of impurity structures in a fraction of the time taken for standard toxicology testing.

In 2014, CDER's work in this area supported the Agency's position in the negotiation of international harmonize-dregulatory guidance on the use of (Q)SAR models. The International Council for Harmonisation M7 regulatory guideline describes how to assess and control DNA-reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk and provides information on appropriate (Q)SAR model selection, interpretation, and reporting [20]. CDER continues to lead the development of best practices for (Q)SAR model application and works closely with other regulatory agencies worldwide to share knowledge and experience to promote regulatory harmonization [21-23, 24]. (Q)SAR modeling under this guidance represents a state-of-the-art approach to toxicity evaluation and its acceptance constitutes a major milestone for the use of modeling and simulation in pharmaceutical development.



In silico modeling-based approaches for predicting toxicity endpoints

Executive summary

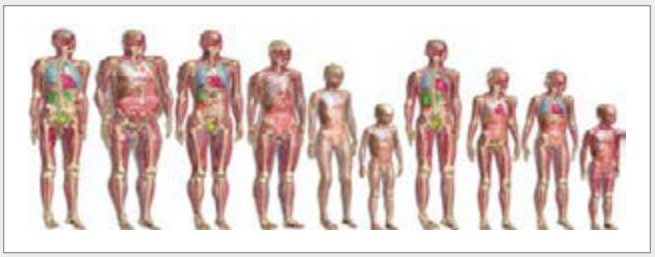
In silico approaches based on (Q)SAR and read-across can prioritize and predict toxicity endpoints, such as toxicokinetics, genetic toxicity, carcinogenicity, developmental toxicity, etc., for a large set of chemicals. Such approaches are being developed in the Office of Food Additive Safety (OFAS) and Office of Applied Research and Safety Assessment (OARSA) in CFSAN to contribute to premarket and/or postmarket safety assessments. These approaches support the FDA's Predictive Toxicology Roadmap by integrating emerging predictive toxicology methods and new technologies into regulatory assessments.

In silico approaches, such as those based on (Q)SAR and read-across modeling, enable rapid and reliable preliminary assessments of hazards and health concerns of chemicals in foods, cosmetics, and other products. At CFSAN, regulatory scientists at OFAS and OARSA are developing and utilizing these approaches for evaluating safety or predicting toxicity of large set of chemicals. The model-based predictions are useful for premarket and postmarket assessments.

OFAS: In OFAS, development, beta-test, and reporting of *in silico* methods are used to prioritize and scale predictions of chemical disposition (intestinal absorption, membrane permeability, distribution, sequestration, toxicokinetics) and chemical toxicity (genetic, carcinogenicity, developmental, teratology). These methods facilitate *in silico* signal-detection of data-gaps, prioritization, risk-ranking, read-across, and reassessments (if mandated) of a large set of chemicals [25]. More recently, these methods were used to report >4.5 million data records for 15,145 organic chemicals that are ingredients in 32 groups of foods, drugs, and cosmetics, and 3,682 colorants assigned to 36 chemical classes [26]. The *in silico* methods are suitable for preliminary premarket review through read-across and identification of structurally similar chemicals with known and/or predicted activities, as well as for facilitating reassessment and addressing postmarket issues.

OARSA: In OARSA, an *in silico* modeling approach based on (Q)SAR model predictions has been used to predict phytochemical absorption, metabolism and hepatoxicity [27]. Increased use of herbal dietary supplements has been associated with adverse liver effects [57, 58]. The composition of phytochemicals used in herbal dietary supplements is complex and most have unknown toxicological properties. A chemical structure database comprising such chemicals associated with human liver injury was established. (Q)SAR models evaluating gastrointestinal absorption were applied and absorbed phytochemicals were used to generate phase I metabolites. Both absorbed phytochemicals and their metabolites were assessed for potential to induce liver injury using (Q)SAR models representing elevated serum enzymes, such as alanine transaminase and aspartate transaminase, to complete an initial safety assessment. The results of this project revealed new potentially hepatotoxic chemicals in herbal dietary supplements and contributed to postmarket regulatory assessment. Such model-based predictions are useful for prioritizing and selecting potentially hazardous chemicals out of a large set for further *in vitro* and *in vivo* testing and revealing and removing hepatotoxic phytochemicals from food products.

Functionalized anatomical models for computational life sciences: from the Virtual Family to o²S²PARC



Executive summary

Over the last 15 years, the Division of Biomedical Physics in CDRH's Office of Science and Engineering Laboratories (OSEL) substantially contributed to the success of computational life sciences in the regulatory environment at FDA. First, it was part of the research consortium that developed the "Virtual Family" (VF), a set of four detailed, anatomically correct, virtual whole-body models of an adult male, adult female, and two children, which has been cited in over 200 regulatory applications for medical devices. The VF was later expanded to the "Virtual Population"; then, these models were physiologically functionalized, allowing coupled electromagnetic-neuronal dynamics modeling in realistic anatomical environments. Within the o²S²PARC and NEUROMAN projects (IT'IS Foundation, Swiss & Korean Governments, NIH, OSEL/FDA), these functionalized models and solvers will be made available on an open-source online platform. o²S²PARC will change the computational life sciences landscape forever, as it will be freely available for researchers worldwide to collaborate and share their developed tools and models without the cumbersome need for hardware or software installation.

Computational life sciences (CLS) and *in silico* tools are the methods of choice to study (i) interaction mechanisms, (ii) device/treatment optimization, (iii) side-effect minimization, (iv) treatment personalization, and (v) closed-loop control for devices that affect organ function through neurostimulation devices. The Virtual Family, with over 1000 citations in peer-reviewed journals, is comprised of detailed, static, anatomical whole-body computer models for medical device safety simulations. It laid the foundation for the "Virtual Population", the MIDA head model, and the NEUROMAN project, which led to the **O**pen **O**nline **S**imulations for **S**timulating **P**eripheral **A**ctivity to **R**elieve **C**onditions (o²S²PARC) project. Since its inception in 2007, the Virtual Family has been cited in over 200 regulatory applications for medical devices and contributed to a more effective, predictable, and comprehensive regulatory process. Though these virtual models represent the anatomical environment, they are insufficient when the biodynamics prevents the separation of the physical dependence upon the anatomical geometry and the physiological response. To overcome this limitation, advanced functionalized anatomical models were developed, dramatically broadening the applicability of CLS in basic research, for the development of novel therapies and devices, and their safety and efficacy assessment. These human phantoms offer high fidelity and detailedness and are empowered with integrated multi-physics solvers and tissue models, optimized for the simulation of physical, physiological, and biological processes in living tissue. Thus, they enable the coupled electromagnetic-neuronal dynamics modeling needed for the development of new neurostimulation devices as pursued by the National Institutes of Health (NIH) SPARC (Stimulating Peripheral Activity to Relieve Conditions) Program and are the core of our vision for designing and implementing the o²S²PARC platform. o²S²PARC is a freely accessible, online platform to host, run, couple, and study all computational models developed across the SPARC community. It integrates the computational models within their natural anatomical environment, permits the integration and coupling of initially disconnected heterogeneous sub-models, and advances interoperability. o²S²PARC applications include exposure evaluations for medical devices which frequently depend on the local, and sometimes large-scale, anatomy. It provides an open-source framework to localize data and models according to their corresponding location within the body and facilitates the identification of components for network and multi-scale computational models.

Risk assessment for transfusion-transmitted variant Creutzfeldt-Jakob disease

Executive summary

Variant Creutzfeldt-Jakob disease (vCJD) is a fatal neurodegenerative disease. FDA's CBER published a risk assessment for transfusion-transmitted vCJD (TTvCJD) in 2014. A computational model was used to estimate the risk of TTvCJD based on information on vCJD prevalence in risk countries, donor travel history and donor deferral policy. The results of the analysis indicate that TTvCJD risk in the US, while highly uncertain, is likely very small. In 2017 CBER reevaluated global geographic vCJD risk and FDA donor-deferral policy in light of global decreasing Bovine Spongiform Encephalopathy (BSE) and vCJD cases. The analysis indicated that a deferral option focusing on the UK, Ireland and France would achieve a level of blood safety like that achieved by the existing policy at the existing policy at that time while allowing more donors to donate.

Four vCJD cases transmitted through red blood cells (RBCs) or a plasma derivative have been reported in the United Kingdom (UK); however, no TTvCJD cases have been reported in the US. In 1999, the US FDA recommended deferring US blood donors who had a history of travel to the UK between 1980 and 1996. The recommendation was expanded in 2002 to include travel to France and other European countries with BSE risk since 1980. In 2012 CBER conducted a risk assessment using a computational mathematical model to estimate the theoretical risk of TTvCJD in the US and the effectiveness of existing donor-deferral policy in reducing TTvCJD risk. The CBER mathematical model described the process starting from donor travel exposure through the steps of donor screening, blood donation, and blood transfusion. CBER scientists used Monte Carlo simulation to incorporate the uncertainty of model inputs for vCJD prevalence, donor travel history, effectiveness of donor questionnaire screening, donation rate and frequency, product usage, and dose-response. Model simulation was also used as a tool to evaluate different donor deferral policy options. Importance/sensitivity analysis was conducted to identify the major risk drivers and data gaps to inform risk control measures and the future direction of research. The results of the 2012 analysis indicated that the TTvCJD risk in the US, while highly uncertain, was likely very small when implementing the donor-deferral policy. CBER published this risk assessment in 2014 [28].

In 2017 CBER reevaluated the global geographic vCJD risk and the FDA donor-deferral policy in light of globally decreasing BSE and vCJD cases [29]. The 2017 analysis indicated an option of a narrower donor-deferral focusing on the UK, Ireland and France only would achieve a level of blood safety like that achieved by the implementation of existing policy, while allowing more donors to donate and simplifying the donor screening process [29]. Based on the results of 2017 analysis, FDA revised the guidance in 2020 to retain donor deferral for three countries with the highest risk of vCJD - the UK, Ireland and France - while lifting donor deferral for all other countries in Europe [59].

In 2022 FDA further revised the guidance to remove donor deferral for vCJD risk, considering the continuously diminishing BSE and vCJD cases worldwide [60].

A risk-informed credibility assessment framework for computational modeling

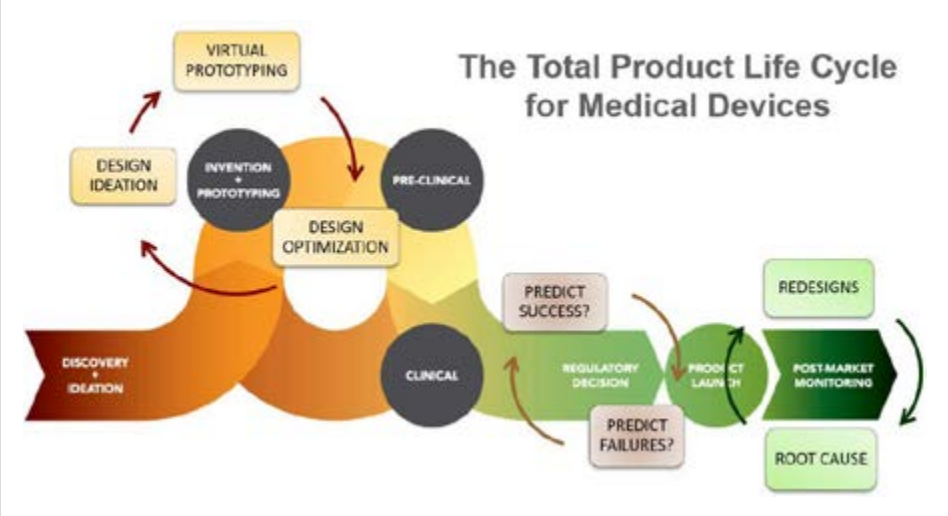
Executive summary

CDRH partnered with multiple stakeholders across medical device industry to develop the American Society of Mechanical Engineers (ASME) Verification & Validation 40 (V&V 40) 2018 Standard, the first consensus standard for evaluating the predictive capability of computational models for medical devices. The standard provides a risk-informed credibility assessment framework that helps an organization or team determine the rigor needed to support using M&S for a particular application. The standard has been adopted by stakeholders in medical devices and drugs, both nationally and internationally. The standard represents a landmark moment for the medical devices modeling community, and the increasing recognition of its utility by other stakeholders suggests it will play a key role in M&S for a broad range of medical products.

Computational modeling employed for medical devices has been successfully utilized early in the ideation stage, supporting pre-clinical evaluations, and for postmarket root-cause analysis and redesigns. Recently, initiatives are underway to fully harness computational modeling throughout the device total product life cycle (see figure), including to support clinical and regulatory decisions. To realize these efforts, the credibility of computer model predictions must be established. Yet, open questions remain: "how much validation?" and "how good is good enough?". The lack of guidance for answering these questions has prohibited broader adoption of M&S in medical products.

In 2011, CDRH formed a working group and aligned with the American National Standards Institute (ANSI) to develop a risk-informed credibility assessment framework, which helps an organization and/or team determine the rigor needed to support using M&S for a particular application. The framework was developed in collaboration with 43 stakeholders, including FDA scientists and regulators, software providers, and the medical device industry (many of which also develop drug products, such as Johnson & Johnson). This standard has broad impact for medical products at FDA due to the nature of the key tenets: the credibility evidence should be commensurate with the risk of using a model for decision-making, and not just by the engineers and analysts, but also management for product-direction decisions, regulatory decisions, and business decisions. The ASME V&V40 Standard [30], after multiple stakeholder engagement activities and an FDA public meeting, was published in November 2018.

The standard has been adopted by internal and external stakeholders in medical devices and drugs, both nationally and internationally. It has been used in scores of medical device regulatory submissions and a handful of CDER Investigational New Drug Applications (IND) and fit-for-purpose applications. These cross-center interactions will position FDA to establish an Agency-wide guidance on using the risk-informed credibility assessment framework for a broad range of computational modeling applications. In acknowledgement of the importance of the standard, the V&V40 working group was recognized with an FDA Group Award in 2019.

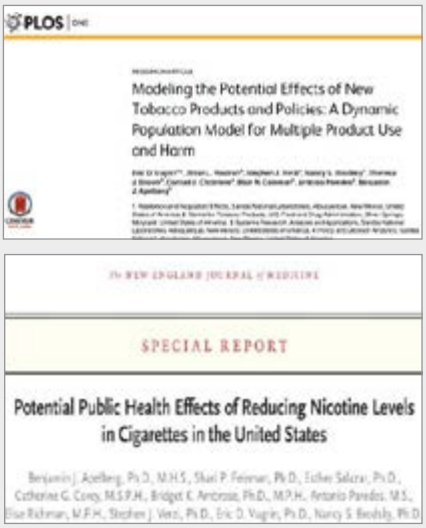


Modeling and simulation in tobacco regulatory science: a case study in system dynamic modeling

Executive summary

The use of tobacco products remains the number one preventable cause of death and disease in the United States. FDA's CTP is responsible for carrying out the Family Smoking Prevention and Tobacco Control Act passed by Congress in 2009. CTP regulates the manufacturing, marketing, and distribution of tobacco products to protect Americans from tobacco-related death and disease. Modeling and simulation are becoming an integral part of many of the activities associated with the development of tobacco regulatory science at CTP. For example, a system dynamic model – coupled with a Monte Carlo simulation approach to mimic uncertainty – was developed by CTP to project the impact of regulatory activities on the US population, including users and non-users of tobacco products. Additionally, modeling and simulation plays a role in the review of regulatory submissions seeking authorization order to market a new tobacco product in the US. For example, modified risk (MR) tobacco applications and premarket tobacco products may include population modeling and simulation methods developed to understand the behavioral and health impact of the products on the US population. Thus, modeling and simulation plays a role in several of the activities associated with the development of tobacco regulatory science at CTP.

The use of system dynamic modeling (SDM) in tobacco research and regulation has a long history with models developed to study different aspects of the tobacco landscape via population dynamics. In the early 2000s, SDMs were developed in which the dynamic of the population was projected based on a system of difference equations (discrete time). Those early models – involving a small number of compartments – were developed to investigate the impact of user behaviors (initiation, cessation, relapse) of single tobacco product (such as cigarettes) on prevalence and mortality. Research and regulatory activities at CTP have opened the door to a new class of models, which can account for the impact of



multiple tobacco products on the dynamic of the population in relation to user behaviors – including poly-use – and health outcomes known to be causally related to the use of tobacco products, including mortality. For example, it is important to understand how potential behavioral responses to the introduction of a new modified risk product (e.g., initiation, switching from cigarettes, dual use) will impact use patterns and tobacco-related disease and mortality. Thus, a well-formulated multi-product system dynamic model can generate valuable evidence associated with these questions that could then be informative in the process of formulating regulatory decisions. In collaboration with Sandia National Laboratories, CTP developed the first system dynamic model to project the impact of regulatory policy on a population using two tobacco products in a tobacco regulatory science environment. Computer implementation of the model includes a component using Monte Carlo simulation to mimic uncertainty and sensitivity analysis [31]. Results from the model were used to support an **advance notice of proposed rulemaking** which would inform the development of a nicotine standard for combusted cigarettes [32]. A MATLAB App was developed implementing a version of the model using Object Oriented Programming. One feature of the App is inclusion of a Gaussian process procedure - via computer experiment using Latin hypercube - for the analysis of univariate outcomes (mortality and prevalence). Another feature is that the App can connect to a High-Performance Computer system.

Advancing model-informed drug development through quantitative clinical pharmacology

Executive summary

The model-informed drug development (MIDD) initiative is CDER's response to fulfilling recent amendments to the Prescription Drug User Fee Act (PDUFA) VI, which aims to further the utilization and potential of model-based approaches to accelerate drug development and thereby patient access to safe and effective drugs. As part of this initiative, the Office of Clinical Pharmacology (OCP) has contributed to the advancement of MIDD through early engagement with drug developers on MIDD-related issues, public workshops, and policy development.

Quantitative models have been used to aid drug development for decades. These MIDD approaches enable prediction of drug pharmacokinetics and pharmacodynamics, and thereby can facilitate decision-making. Quantitative models have been routinely applied to optimize dosing in the general population or patient subgroups and inform the design of clinical trials [33]. Given the utility of MIDD, these approaches have the potential to accelerate drug development and patient access to safe and efficacious medicines.

Recognizing this potential, the FDA was charged with advancing MIDD in PDUFA VI. In response, CDER's MIDD initiative was established. The multipronged initiative includes policy development, stakeholder engagement, education/training, and research. OCP is heading the MIDD pilot program, which enables the early engagement of regulators and drug developers on MIDD strategy issues to maximize the potential for model-based approaches. As of December 2021, 58 meeting requests from 28 sponsors were received and 46 sponsor meetings have been conducted (up to 2 meetings conducted per meeting request granted). Submissions received via the MIDD pilot program include both widely-accepted and newly emerging methodologies that can be applied to various topics in drug development such as dosing and trial optimization. These efforts have had direct implications on individual clinical development programs, providing early alignment on a regulatory path forward using MIDD [34].

As part of stakeholder engagement efforts, OCP partnered with FDA's Oncology Center of Excellence and the International Society of Pharmacometrics to host a workshop on MIDD in oncology. This workshop stimulated discussions across academia, industry, and regulatory scientists on not only how MIDD can be used to accelerate the development of oncology drugs but how it has the potential to shift the treatment paradigm towards using an optimized dose instead of a maximum tolerated dose [35]. OCP, in collaboration with CBER, hosted a workshop on PBPK with the aim of identifying best practices and research needed to advance this approach [36].

Accumulated knowledge and regulatory experience with long-standing MIDD approaches have led to the revision of current guidance documents including the population pharmacokinetic and exposure-response guidance documents [61, 62]. These revisions aim to provide clarity on sponsor expectations and increase consistency and transparency in regulatory review. A consensus approach to model evaluation may be considered in the future for harmonization across FDA.

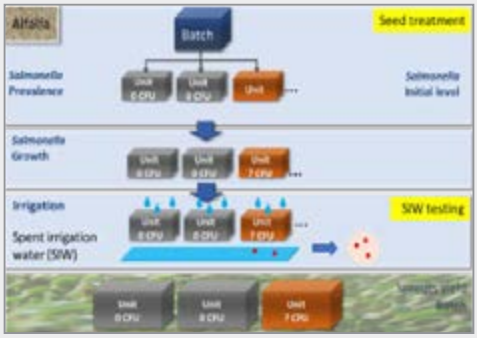
Revealing food safety risks and evaluating potential preventive controls and mitigation strategies: quantitative risk assessment models

Executive summary

The FDA develops and makes publicly available innovative models that connect food safety concerns and risk management options to predicted public health outcomes. The results of these risk assessment models provide the Agency, food industry, and consumers with critical information needed to develop food safety and nutrition policies and practices, implement these policies, and investigate postmarket events such as foodborne illness outbreaks or contamination. Examples of FDA models include a retail food establishment model evaluating strategies to reduce the potential for norovirus transmission, a production level model evaluating strategies to reduce the potential for *Salmonella* contamination of sprouts, and a farm level model evaluating strategies to reduce the risk of pathogenic *E. coli* contamination of fresh produce. These models informed policy decisions associated with the FDA Food Code, FSMA Preventive Controls and FSMA Produce Safety Rules and Guidance. Additional recent efforts have focused on developing modeling frameworks to better inform investigations of root cause for foodborne outbreaks in real-time and to evaluate health outcome trade-offs (risk-risk and risk-benefit). As these examples illustrate, FDA risk assessment models are focused and fit for purpose, helping to utilize the best science to solve our most pressing food safety and nutrition problems.

The FDA continues to develop a suite of innovative models that predict public health outcomes associated with a variety of food safety concerns and risk management strategies. These models inform policy development, policy implementation, and post-market investigations. For example, FDA developed a probabilistic discrete event model [37] to explore norovirus transmission in retail food establishments. This model serves as a decision-support tool for risk managers to improve consumer protection through updates to the FDA Food Code. Norovirus is a leading cause of foodborne illness globally and within the United States [38-40]. Restaurants are the most common setting of reported norovirus foodborne illness outbreaks resulting from food preparation in the United States [41]. Results revealed that compliance with exclusion from work of symptomatic food employees can be more impactful than extending the length of exclusion because infectivity (and virus levels) is largest during the first days of illness. As a result, the Agency decided not to increase the exclusion period at this time and to instead focus on compliance with and adoption of current Food Code recommendations. Results also identified improved efficiency and compliance with hand hygiene practices as particularly impactful, thereby flagging potential areas for increased effort.

The production level *Salmonella*-alfalfa sprout model [42] is an example of a quantitative model FDA developed to inform FSMA guidance. This model predicts growth and spread of pathogen contamination originating in sprout seeds and estimates the risk reduction arising from seed treatment and/or spent sprout irrigation water (SSIW) testing. As with all FDA models, the best available relevant scientific data and risk modeling methods were used to build the model. The predictive model captured variability in data and uncertainty in model parameters and characterized risk estimates with attendant uncertainties. When SSIW testing is implemented in combination with seed treatment, the model predicted a greater degree of risk reduction than that from using either intervention alone. When SSIW testing is used alone, results indicate that a larger proportion of sprout batches would have to be removed from production due to contamination. The model quantified the impact on risk of SSIW coverage, identifying the importance of ensuring tested SSIW is drawn from all areas of the sprout batch. A web-based user-friendly model interface was created to facilitate further exploration of scenarios by interested parties among the Agency, industry, and consumers.



Complex innovative trial design pilot program

Executive summary

The Complex Innovative Trial Design (CID) Pilot Program is designed to facilitate and advance the use of highly innovative clinical trial designs with a particular focus on designs for which simulations are necessary to determine trial operating characteristics. This joint CDER and CBER pilot meeting program provides requesting sponsors that are selected into the program two meetings to discuss proposed CIDs with FDA experts. The CID Pilot Program fulfills a performance goal agreed to under the Prescription Drug User Fee Act (PDUFA) VI.

The Complex Innovative Trial Design (CID) Pilot Program is a joint CDER and CBER program which is part of FDA's ongoing commitment under the Prescription Drug User Fee Act (PDUFA) VI to enhance FDA's capacity to review CIDs [43]. The trial designs contemplated under the pilot program include, but are not limited to:

- Complex adaptive designs,
- Bayesian designs (including the possibility of an informative prior),
- Other novel designs [44]

As stated in the August 30, 2018, *Federal Register* notice [44] announcing the program, "Initial priority will be given to trial designs for which analytically derived properties (e.g., type I error) may not be feasible and simulations are necessary to determine operating characteristics." Simulations are thus key to the CID Pilot Program. A detailed simulation plan and report are expected as part of the CID meeting request and meeting package submissions, respectively. Such a simulation report should include:

"a. Example trials in which a small number of hypothetical trials are described with different conclusions.

b. Description of the set of parameter configurations used for the simulation scenarios, including a justification of the adequacy of the choices.

c. Simulation results detailing the simulated type I error probability and power under various scenarios.

d. Simulation code that is readable, adequately commented on, and includes the random seeds. The code should preferably be written in widely-used programming languages such as R or SAS to facilitate the simulation review." [44]

Anticipated benefits to sponsors include increased interactions with experts from CDER or CBER. With the mutual agreement of the sponsor and FDA, crucial study design characteristics (adaptive, Bayesian), simulation objectives, and modeling characteristics, may be publicly disclosed "to promote innovation and to provide better clarity on the acceptance of different types of trial designs..." [44]. Eligibility factors for the CID Pilot Program may be found on the FDA CID Pilot Program **webpage** [45]. The pilot program has been successfully underway for years and FDA has published case examples of trials admitted into the program on the CID Pilot Program webpage [46].

Maximizing the public health impact of FDA actions: risk-based, data-driven decision analysis models

Executive summary

FDA has innovatively developed risk-based, data-driven decision analysis models to inform decision-making for policy development and resource allocation. This decision analysis modeling approach was applied to numerous applications including risk management of animal drug residues in milk and milk products, a prioritization of foods requiring additional traceability requirements (FSMA), and prioritizing surveillance sampling and inspections. Decision analysis models are particularly useful when there are many alternatives to prioritize and data informing the decisions are not readily combined or compared. The use of a decision analysis framework provides FDA with a structured and transparent decision process that considers a wide diversity of knowledge and enables FDA to maximize public health impacts within resource constraints.

The FDA developed a suite of modeling tools to inform policy development and resource allocation for the foods program. An example is a multicriteria-based ranking model [47] for risk management of animal drug residues in milk and milk products. This model serves as a decision-support tool for re-evaluating which animal drug residues should be considered for inclusion in milk testing programs. FDA undertook this project in response to a request from the National Conference on Interstate Milk Shipments (NCIMS), a coalition of federal and state governments and Puerto Rico, the dairy industry, academia, and consumers. A key question is whether residues of animal drugs other than beta-lactam antibiotics – currently the focus of milk-sampling programs – warrant monitoring.

The modeling tool integrates a variety of data that collectively contribute to a risk score for each drug tested including: (1) the likelihood that the drug would be administered to lactating dairy cows; (2) the likelihood that drug residues would be present in milk (bulk tank or bulk milk pickup tanker); (3) the relative extent to which consumers could be exposed to drug residues via consumption of milk and milk products (including impact of processing); and (4) the potential for an adverse human health effect following dietary exposure to the drug residue. Since the model was released, the NCIMS initiated a pilot project exploring the utility of sampling bulk tank milk for other drug residues, selecting specific drugs from those that ranked high in the model. The implementation of this tool has the potential to protect US consumers from unnecessary exposure to antibiotic drug residues in dairy products.

Each year, as part of the work planning process, FDA must prioritize which foods, facilities, and farms to sample or inspect, and which concerns to address. Increasingly, the Agency is using data-driven, risk-based models to rank options based on public health risk criteria and prioritize the options by operational and policy-related decision factors integrated with constraints. These models include a wide diversity of relevant data such as information about recent foodborne outbreaks and recalls, recent sampling and inspection results, consumption data, and properties of the foods and hazards that inform the potential risk of adverse health effects for consumers. Application of these models have demonstrated improved risk-based targeting and provided efficiencies in the annual work planning process.

These risk-based resource allocation models were developed using a suite of software platforms and increasingly utilize interfaces that facilitate data and result updates, sensitivity analysis, data and result visualization and analytics, and modification of model structure or constraints, as required. New directions include incorporation of machine learning and artificial intelligence and utilization of new (big) data streams, as these become available.

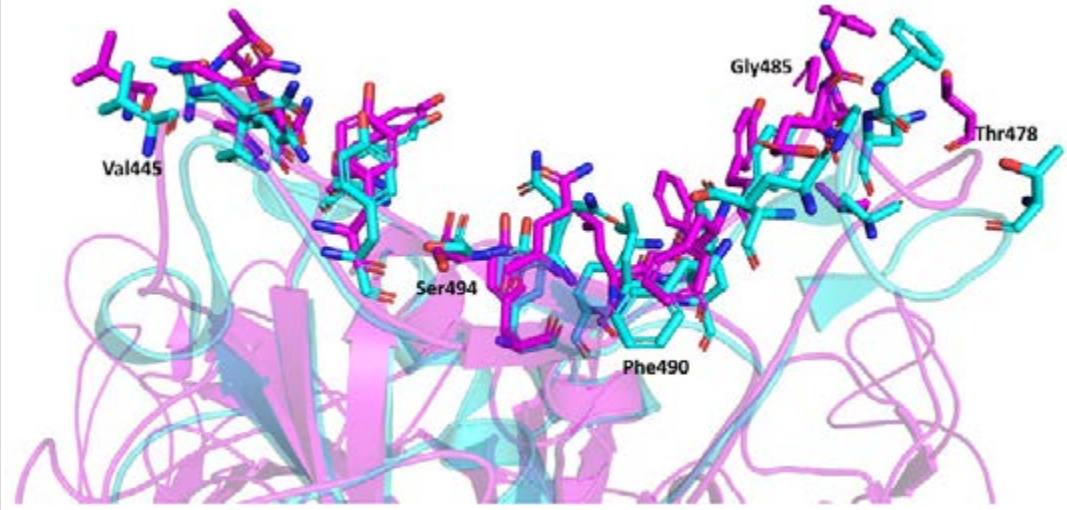
Homology modeling and molecular dynamics simulations to elucidate interactions between SARS-CoV-2 trimeric spike protein and ACE2

Executive summary

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). Understanding the interactions between the SARS-CoV-2 trimeric spike protein and its host cell receptor protein, angiotensin converting enzyme 2 (ACE2), is important for developing drugs and vaccines to prevent and treat COVID-19. We identified the critical residues in the spike protein that interact with ACE2 using homology modeling and molecular dynamics simulations. The identified interacting residues provide new insights to understand the mechanisms of SARS-CoV-2 infection and can facilitate the development of drugs and vaccines to prevent SARS-CoV-2 infection and to treat COVID-19 patients.

SARS-CoV-2 causes COVID-19. It is important to develop drugs and vaccines to combat COVID-19. The spike protein plays a major role in viral infection by binding to ACE2, allowing the virus to enter the host cell. The atomistic structure of the full length wild-type trimeric spike protein complexed with ACE2 could help identify drugs for COVID-19. Hence, homology modeling and molecular dynamics simulations were used to build the trimeric form of the spike protein complexed with human ACE2 and to characterize the interacting residues at the interface [48]. As shown in figure below, the interactions between the full-length trimeric spike protein and ACE2 are different from those between the RBD and ACE2. The elucidated interactions are expected to help facilitate the development of drugs and vaccines to prevent SARS-CoV-2 infection and to treat COVID-19 patients [48].

FDA has been working closely with the public and private sectors to identify drugs to keep Americans safe from COVID-19. The interacting residues of SARS-CoV-2 spike protein could accelerate the development of drugs to treat COVID-19 patients. The developed spike protein structure not only paves the way for screening FDA-approved drugs for potential repurposing to treat COVID-19, but also has been used in the design of epitopes for potentially new COVID-19 vaccines.



Superimposition of the spike protein-ACE2 complexes using the full-length trimeric spike protein (Magenta) and the truncated spike protein RBD monomer (Cyan). The interacting residues are represented by stick model illustrations, while the rest of the ACE2 proteins are depicted in ribbon model form. The five new interacting residues identified using the full-length trimeric spike protein complexed with ACE2 are labeled.

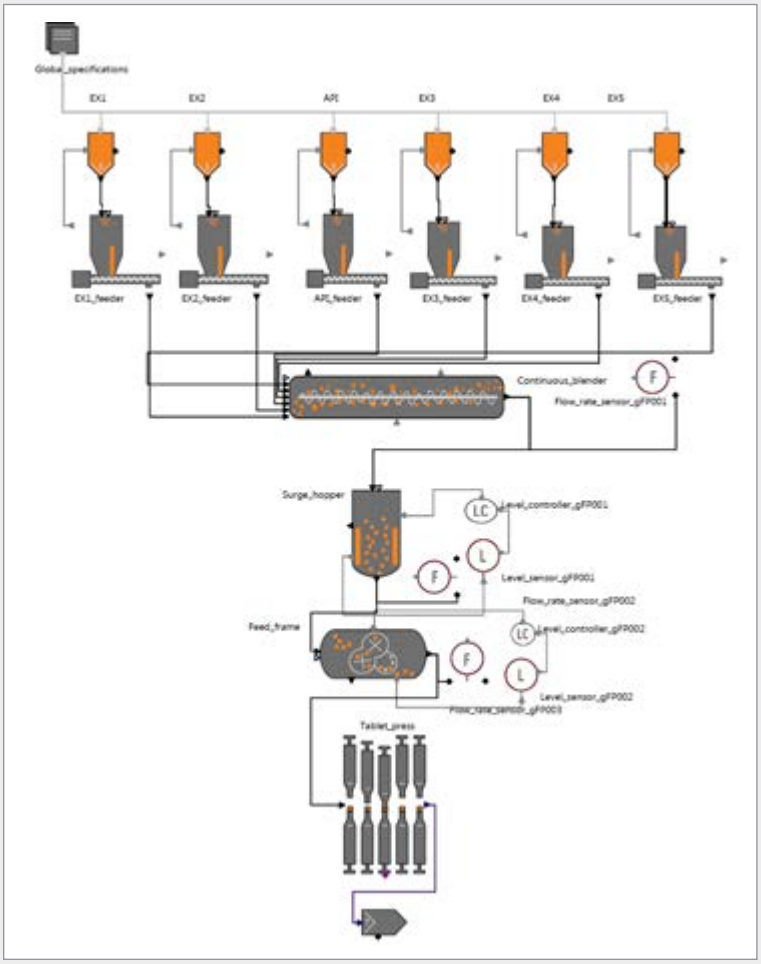
Modeling and simulation-guided premarket product quality assessment

Executive summary

The adoption of continuous pharmaceutical manufacturing has been a driving force for the growing utilization of modeling and simulation for risk assessment, process design, and control strategies. FDA is embracing the digitalization trend, starting to develop and utilize digital twins that can provide an *in-silico* representation of the entire continuous pharmaceutical manufacturing process. A digital twin of a continuous manufacturing line provides reviewers with a powerful tool to assess sensitivities of material attributes and process parameters, reliability of control strategies, and effectiveness of mitigation plans for potential disturbances.

CDER has developed the capability to create digital twins of continuous manufacturing processes to support the quality assessment of such processes. These efforts have resulted in several internal reports and external publications. The knowledge and tools have been shared with the broader agency stakeholders in the form of technical consults and a training course.

A digital twin is an integrated multi-physics, multiscale, probabilistic simulation of a complex system and uses the best available data, sensors, and models to mirror the behavior of its corresponding twin. A fully developed digital twin consists of a physical component (e.g., unit operations), a virtual component, and automated data communications between the two. The virtual component consists of a collection of models to perform real-time simulation of the physical component and conduct system analyses, such as sensitivity analysis, design space and feasibility studies, and system optimization [63]. The models can be mechanistic, data-driven, or hybrid models which are built on process knowledge and understanding, historical data, and real-time data collected from the physical component to capture the fidelity of the physical space.



Since 2019, CDER has developed digital twins of the continuous manufacturing lines for several solid oral drug product regulatory submissions. The digital twins were utilized to i) demonstrate how modeling and simulation can be used for quality assessment including risk assessments and control strategy evaluations (e.g., material feeding control limits, material diversion approaches); ii) compare product quality risks and control strategies among the submissions; iii) support the assessment of process models submitted by sponsors as part of the proposed control strategy; and iv) support workforce development for advanced manufacturing by providing reviewer training where the models are utilized to visualize comparisons between different processes and control strategy approaches [64, 65]. The development and application of digital twins are now being extended to API manufacturing and complex products.

Opportunities

Figure 1 in Section 2, *Modeling and Simulation at FDA*, provided insight into potential opportunities for advancing M&S at the FDA and within FDA regulated industries. Further opportunities were identified by surveying FDA staff engaged in modeling and simulation. This final section of the report discusses these opportunities. Some of the opportunities are applicable to the entire Agency, while others are specific to certain FDA Centers or to certain M&S disciplines (e.g., environmental toxicology, toxicokinetics, food safety risk assessment, big data and machine learning).

M&S Opportunities for the Agency

M&S Applications

A snapshot of the different applications of M&S at FDA is captured in Figure 1 (Section 2, Page 5), where each square represents one modeling discipline and one FDA regulatory application area; the color of the square denotes the FDA Center. One opportunity is to **accelerate the use of modeling in the product development and premarket review stages,** where appropriate, in Centers or applications where it is not well established. This may deliver substantial public health impact, and lessons learned in establishing reliable M&S approaches for these stages may enable rapid M&S solutions to be developed for other regulatory problems. Lack of "Good Simulation Practices" guidelines may be one of the limiting factors for broader use and acceptance of M&S. Creating these guidelines is a key opportunity for the Agency to have an important leadership role.

Regarding the modeling disciplines, presented on the left side of Figure 1, there are areas where we do not have information on how specific M&S disciplines are not being used (i.e., the white squares). No single modeling discipline is being used by every Center. There may be good reasons why a particular modeling discipline is not used by a Center and some applications may not have been captured by the survey, but this figure challenges us to consciously determine whether there are additional ways in which M&S could play a meaningful and impactful role in FDA's regulatory mission, but currently does not potentially due to various reasons such as lack of sufficient subject matter expertise, guidelines related to application of M&S in regulatory submissions, or M&S technological capabilities. **Fully understanding these gaps is another important opportunity for the Agency**. This could further support key regulatory science efforts, as indicated in the FDA Strategic Plan for Regulatory Science [49].

Opportunities to Support FDA Scientists

Two key opportunities that could directly support FDA scientists have been identified. The first opportunity is to **strengthen internal networks for sharing resources and modeling techniques (e.g., model building, validation, and application), to host training sessions to enhance hands-on experience with these resources, techniques and relevant software platforms**, and to promote better understanding and harmonization amongst FDA stakeholders.

The second opportunity is to **consider the establishment of Good Simulation Practice to foster harmonization across the FDA, and where appropriate, with international regulatory bodies**. Establishing best practice and quality control principles to ensure more harmonized standards for model development, model use and validation, would strengthen our current modeling and simulation practices. It is also critical to develop a common set of expectations or guidelines for model verification, validation, credibility assessment and maintenance between industry and regulators, as well as between regulatory scientists/modelers and reviewers within the FDA. Further publication and/or usage of relevant guidance documents (e.g., International Council on Harmonization items Q13 and M7 [50,20], and the International Medical Device Regulators Forum on Software as a Medical Device [51]) will promote better alignment on best practices and expectations between stakeholders.

Other Opportunities Relevant to all Centers

Three other major multi-Center opportunities were identified. M&S is now increasingly used by industry in process analysis and improvement. There is great potential for **using M&S to enhance FDA's submission process and workload prediction to aid research optimization and resource allocations**.

Table 1 – M&S Opportunities relevant to the entire Agency

1. Accelerate the use of modeling in the product development and premarket review stages, where appropriate
2. Identify current gaps where M&S could play a meaningful and impactful role in FDA's regulatory mission, but currently does not due to lack of scientific expertise, personnel resources, regulatory guidelines, or knowledge of M&S technological capability
3. Harness FDA partners and collaborators (e.g., CERSIs, NIH IMAG group, NSF IUCRC Program) to advance external M&S efforts relevant to FDA's mission
4. Strengthen internal networks for sharing resources and modeling techniques within FDA and host training sessions to enhance hands-on experience with these resources, techniques and relevant software platforms
5. Consideration of the establishment of Good Simulation Practice to foster harmonization across the FDA, and where appropriate, across international regulatory bodies
6. Use M&S to enhance FDA's submission process and workload prediction to aid research optimization and resource allocations
7. Harness integrated approaches that use multiple modeling disciplines and rely on data from multiple sources
8. Use interactive data visualization capabilities to improve engagement with stakeholders

For example, natural language processing and machine learning approaches have been used to predict FDA review time of devices submitted under the 510(k) pathway [52].

Secondly, there is an opportunity to more fully **harness integrated approaches that use multiple modeling disciplines and rely on data from multiple sources**, such as approaches integrating (Q)SAR and PBPK methods, or IVIVE and PBPK methods (see Figure 1 caption for explanation of acronyms). Integrating M&S disciplines is particularly useful for scenarios where there are substantial data gaps. Integrating mechanistic or physics-based models with statistical or machine-learning-based models, to take advantage of the power of both methods, will likely be an especially effective method for difficult problems.

Lastly, **interactive data visualization capabilities** have advanced in recent years and have been utilized by industry, the media and others to better present complex information or large amounts of data. However, these methods are not yet widely utilized by FDA and represent an incredible opportunity to improve FDA engagement with stakeholders.

A summary of all opportunities discussed in this sub-section is provided in Table 1.

Opportunities for FDA Centers and/or M&S Disciplines

Various other opportunities were identified from surveying ModSimWG membership, that were either specific to certain Centers because they were relevant to regulation of specific products, or specific to certain types of modeling disciplines. These opportunities are presented in Table 2. This table should be considered a sample of Center- or discipline-specific M&S opportunities, rather than a comprehensive list. As discussed above (Table 1, item 2), there will likely be numerous other potential ways that M&S could be used at FDA. It is hoped that the ideas presented in Table 2, and this report, provokes consideration by FDA staff, collaborators, and other stakeholders into how FDA can continue to capitalize on the power of M&S in protecting and promoting public health.

Table 2 – Opportunities for specific Centers and/or modeling disciplines

Purpose of M&S Opportunity	Description	Relevant modeling disciplines	Primary Centers impacted
To replace or augment clinical trials with *in silico* clinical trials	Develop M&S methods and frameworks for evaluating medical products using virtual cohorts of patients, sometimes referred to as *in silico* clinical trials. *In silico* clinical trials can be used to evaluate medical products when real clinical trials would be unethical (e.g., using the Virtual Family to assess thermal safety of implanted devices during MRI – see page 11), augment and potentially reduce the required size of clinical trials (see [53,54]), or ultimately even replace clinical trials.	Many	CDER CDRH CBER
To reduce the need for clinical studies to support bioequivalence	Use M&S to inform product specific guidance development for bioequivalence of complex locally-acting drug products, such as dermal and ophthalmic topical products and orally inhaled and nasal drug-device combinations. *In vitro* experiments supported by M&S may be used to develop product-specific bioequivalence approaches that do not include comparative clinical endpoint or pharmacodynamic studies.	Fluid dynamics, physiologically-based pharmacokinetic modeling	CDER
To provide evidence supporting safety or effectiveness of medical imaging devices and computer-aided diagnostic software	Leverage radiation transport simulations to generate evidence that can assist in the regulatory process for medical imaging devices and computer-aided diagnostic software. Industry already invests heavily in developing tools that can simulate radiological devices for internal R&D. There is an opportunity to use these tools in the regulatory process, especially for submissions which do not normally require clinical data (e.g., some 510(k) devices).	Radiation transport	CDRH
To provide a novel method for medical device manufacturers to support reprocessing	Investigate feasibility of, and if appropriate encourage the use of, M&S in medical device regulatory submissions as evidence supporting device sterilization or reprocessing (cleaning, disinfecting, sterilizing) effectiveness.	Fluid dynamics, solid mechanics, thermal	CDRH
To provide a quantitative comparison of the public health impact of different risk mitigation strategies	Modeling and simulation approaches to compare risk mitigation strategies intended to reduce the transmission and, ultimately, the burden of disease associated with infectious pathogens, including creating interactive applications that allow industry, consumers, and other stake-holders to explore potential strategies.	Quantitative risk assessment, machine learning, agent- based, discrete event modeling	CBER CFSAN CDER
To utilize M&S capabilities to predict health risk estimates in data-scarce populations	Population-based PBPK and BBDR dose-response modeling for real-life chemical risk exposure estimates in a specific population (mechanistic modeling).	Physiological modeling and variability analysis	NCTR

To improve our ability to determine root cause in foodborne outbreaks	Develop an outbreak investigation tool that allows FDA investigators to easily test hypotheses regarding the root cause of an ongoing or recently completed foodborne outbreak. Tool would leverage quantitative agent-based or discrete event models of food production and use machine learning to create an interactive environment for investigators.	Quantitative risk assessment, machine learning, agent- based, discrete event modeling	CFSAN
To utilize M&S capabilities in veterinary medicine applications	Enhance the understanding of impact of veterinary drugs on dose-response relationships by utilizing mechanistic modeling approaches based on *in vitro* data by: • Supporting research for model development • Exploring species-specific idiosyncrasies (including the effect of environment, breed, genetic polymorphisms, disease, and food) • Identifying potential formulation effects (absorption, pre-systemic metabolism, and *in vivo* dissolution)	Mechanistic modeling (PBPK, IVIVC, IVIVE, IVIVE, etc.)	CVM
To improve the quality of regulatory safety assessments of substances in food, drugs, and environmental chemicals	Risk assessment modeling applications including: • Incorporating information on post-market adverse events (The FDA Adverse Event Reporting System (FAERS)) for food safety evaluations • Applying probabilistic modeling to characterize exposure and risk associated with chemical and microbial hazards in food • Using quantitative analysis of uncertainty and variability in probabilistic risk models • Basing risk management solutions on ranking and prioritization of food commodities, hazards, and decision alternatives • Incorporating mechanistic information, such as predictions of fate and transport modeling, from research projects into risk assessments for making regulatory decisions • Using (Q)SAR models in combination with a standardized framework for the integration of *in silico* and empirical toxicology data to support risk assessment	Risk assessment, mechanistic modeling, (Q)SAR	CFSAN NCTR CDER
To expand the application of big data and machine learning approaches to predict effects of different types of substances including drugs, environmental chemicals, etc.	Predictive modeling approaches including: • Network analysis (neighbor-edges based and unbiased leverage algorithm – sNebula [55]) to analyze sparse big data • Predicting toxicity endpoints such as immunotoxicity of drugs and enable better utilization of ToxCast data for risk assessment • Novel machine learning methods such as “Decision Forest” (based on chemical structures, and genomic, genotyping and proteomic data) to improve predictive performance and enable prediction confidence analysis and application domain assessment [56].	Big data, machine learning, risk assessment	CDER NCTR CTP

To curate quality data and manage data standardization in support of reliable *in silico* chemical tools development	Endocrine disruptor knowledge base (EDKB) – allows regulatory researchers to quickly access ED data from multiple assays for specific or similar compounds to estimate the estrogenicity potential of a new chemical entity.	Database development, chemical modeling	NCTR
To curate quality data and manage data standardization in support of reliable *in silico* chemical tools development	Estrogenic Activity Database (EADB) - Most comprehensive public database of chemicals assayed for estrogenic activities available for regulatory use.	Database development, chemical modeling	NCTR
To improve the ability to predict clinical adverse effects of drugs and chemical constituents based on non-clinical testing and modeling	Develop and apply complementary *in silico* modeling approaches that predict: • Off-target molecular target binding profiles based on chemical structure • (Q)SAR models trained on non-clinical, organ-specific toxicology data linked to clinical adverse effects • Clinical pharmacological effects based on combined inputs from *in vitro* data (e.g., predicting clinical ECG from individual cardiac ion channel inhibition data)	AI/machine learning, (Q)SAR, physiological	CDER CTP
To forecast produce contamination potential	Develop a forecasting model to inform regulators and produce industry about the potential location and timing of contamination events based on geospatial, environmental, climatic, and production activities.	Geospatial, statistical, Bayesian, Big data, AI	CFSAN
To support the application of novel technologies to improve product manufacturing and quality	Evaluate advanced manufacturing technologies that can enhance the quality and availability of drug substances or products utilizing model-based digital twins.	Mechanistic models, AI/machine learning	CDER
To achieve focused and optimum targeting of most risky products as part of post market vigilance	Develop M&S methods and frameworks for evaluating risk of products for optimum targeting and collection. It is critical to be able to focus the agency's limited resources on inspection and testing of most risky products to maximize public health protection. Post market vigilance and testing becomes especially important for import products since access to their manufacturing facilities may be difficult. M&S methods can help inform optimum collection strategies to achieve statistical sampling of large, heterogeneous shipments which in turn enhances probability of uncovering violations in regulated products.	Quantitative risk assessment, machine learning, agent-based, discrete event modeling	ORA CFSAN CDER

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