FDA's Predictive Toxicology Roadmap

2018 Annual Report

Prepared by the Food and Drug Administration's Toxicology Working Group

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Executive Summary

FDA's Predictive Toxicology Roadmap was published in December 2017 by the Food and Drug Administration's (FDA's) Toxicology Working Group. It describes FDA's current thought on viable ways to foster the development and evaluation of emerging toxicological methods and new technologies and incorporate them into FDA regulatory review, as applicable.

This six-part framework outlines Agency priorities and engagement in predictive toxicology, emphasizes the importance of the context of use, and identifies toxicology issues related to FDA-regulated products. FDA's Predictive Toxicology Roadmap also identifies the toxicology areas that could benefit from improved predictivity as well as promising new technologies that could potentially meet these needs and support animal 3Rs (Replacement, Reduction, and Refinement).

Toxicology-related areas that FDA scientists have been working on include microphysiological systems (MPS), computational toxicology, and in vitro alternative methods. Moreover, FDA has been involved in collaborative projects related to advancing predictive toxicology with the International Council for Harmonization (ICH), the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), and the Organisation for Economic Co-operation and Development (OECD) Test Guidelines Programme (TGP). FDA also participates on the Regulatory Panel for the alternative research conducted through the European Union ToxRisk consortium, a public–private partnership under the EU Horizon 2020 program.

The Toxicology Working Group developed a list of 2018 activities that support implementation of the Predictive Toxicology Roadmap. Some sections like presentations

and workshops may include one-time events. Moreover, research work includes projects that were completed or ongoing by the end of 2018. Many activities address several key components of the Predictive Toxicology Roadmap, such as continued communication, collaboration, training, and research. Consequently, the following sections represent implementation of multiple aspects of the Predictive Toxicology Roadmap.

Research

Through a variety of research projects conducted by FDA product centers, cross-center partnerships, or broader collaborative activities with our stakeholders, FDA has been working to identify scientific needs, pursuing a better understanding of the new alternative technologies, and assessing the opportunities and challenges of their applicability to improve the predictivity of safety and risk assessment.

- **The Comprehensive in vitro Proarrythmia (CiPA) research program** is using advanced in vitro electrophysiology methods to directly address issues related to proarrhythmia risk of drugs. Additionally, the in vitro data is used to provide experimentally verified parameters and constraints to improve the in-silico cardiomyocyte model development (FDA's Center for Drug Evaluation and Research (CDER)).
- **Tissue chip technology** has been explored and evaluated for product center-specific endpoints, including pharmacology− and toxicology−specific assessments (FDA's Center for Biologics Evaluation and Research (CBER), CDER, FDA's Center for Devices and Radiological Health (CDRH), FDA's Center for Food Safety and Nutrition (CFSAN), FDA's Center for Veterinary Medicine (CVM), and FDA's National Center for Toxicological Research (NCTR)). Also, CVM has worked with CFSAN and the University of Maryland to investigate organ-on-a-chip models that address the potential impact of residues of veterinary drugs on the human gastrointestinal microbiome.
- CVM experts are working with NCTR researchers to optimize the standard in vitro mammalian genotoxicity assays for evaluating engineered nanomaterials.
- CVM has established a research collaborative agreement to investigate the application of in silico toxicological tools (MULTICASE) in evaluating new animal drug applications.
- FDA experts supported review of a transcriptional biomarker for genotoxicity assessment related to cancer risk (via the CDER Genetic Toxicology subcommittee with ad hoc members that included experts from other FDA product enters).

- **Examples of NCTR's ongoing research to support FDA's Predictive Toxicology Roadmap**:
  - Rat Blood-Brain-Barrier-on-a-chip model to study traumatic brain injury.
    Principal Investigator: Syed Ali (NCTR)
  - A Comprehensive Characterization of iPSC-CMs Models for Drug-Induced Arrhythmia Using High Throughput Screening Assays.
    Principal Investigator: Li Pang (NCTR, cross-center collaboration)
  - Evaluation of an in vitro testis organ system as an alternative model for male reproductive toxicology.
    Principal Investigator: Noriko Nakamura (NCTR, cross-center collaboration)
  - Development of an in vitro system to evaluate the disease-related toxic effects of inhaled test agents in human airway tissue models.
    Principal Investigator: Xuefei Cao (NCTR, cross-center collaboration)
  - Development of a multi-pathway physiologically based pharmacokinetic (PBPK) model for nicotine in humans.
    Principal Investigator: Xiaoxia Yang (NCTR, cross-center collaboration)
  - 3D-QSDAR model to predict hERG inhibition of drugs that are showing clinical signs of cardiotoxicity.
    Principal Investigator: Svetosla Slavov (NCTR, external collaboration)
- **The Expanded Decision Tree (EDT)/Threshold of Toxicological Concern (TTC)** was developed by the Office of Food Additive Safety (OFAS) to categorize chemicals into toxicity classes and to establish a TTC for each class. Drs. Szabina Stice and Timothy Adams gave several talks on this work in 2018, including to the European Food Safety Authority, the World Health Organization's Joint Expert Committee on Food Additives, the U.S. Department of Agriculture, and the Interagency Risk Assessment Consortium. (CFSAN)
- CFSAN is evaluating the impact of dog studies on decisions about the safe use of food and color additives.

- In Silico Prediction of Metabolism and Toxicity of Flavors and Additives in Electronic cigarette e-liquids and aerosols.
  (Ongoing Commissioner's Fellow project, Center for Tobacco Products (CTP))
- Genotoxicity Assessment of Flavoring Ingredients in ENDS Products.
  (CTP research project)
- Development of a multi-pathway physiologically based pharmacokinetic (PBPK) model for nicotine in humans.
  (CTP research project, cross-center collaboration)
- Development of a Software Platform (SPECTRE) to Inform Health Risk Evaluation of ENDS Constituents.
  (CTP research project, cross-center, external collaboration)

Workshops

To continue the dialogue with our colleagues and experts in the field, FDA either hosted, co-led, or participated in many scientific workshops. We encourage continued communication, collaboration, and scientific knowledge exchange to support our regulatory mission.

The following events are relevant to implementing FDA's Predictive Toxicology Roadmap.

- Public Hearing on the FDA Predictive Toxicology Roadmap (September 2018)
- FDA-IQ-NCATS Strategy Meeting for Clinical Trials on a Chip (September 2018)
- Session on Pathways Toward Regulatory Use, the 13th NIH Tissue Chip Consortium Meeting (September 2018)
- International Workshop on Genotoxicity Testing (IWGT)
  - Co-led an international group on in silico analysis of genotoxicity data that looked to potential future use of in silico analyses as a tool (CDRH)
  - Participated in an international group using in silico analysis ("big data") that led to a change (fewer needed strains) in the recommended test battery for the standard Ames assay (bacterial reverse mutagenesis)

- FDA's Oncology Center for Excellence/AACR workshop: Nonclinical Models for Safety Assessment of Immuno-oncology Products (September 2018)
- FDA/CDER-HESI Workshop on Preclinical and Translational Safety Assessment of CD3 Bispecifics (October 2018)
- NIH Workshop *the Monocyte Activation Test for Pyrogen Testing of Medical Devices* cohosted by NICEATM and PISC: CDRH presentation *The FDA MDDT Program and Considerations for MAT Testing of Medical Devices* (September 2018)

Guidance

Recent new, draft, or revised guidance documents published by FDA, such as those listed below, incorporate new toxicology approaches. These approaches can provide better predictive data and support the 3Rs.

- Draft Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (July 2018) [Revision of the Nov 2006 guidance] (CBER)
- Draft Guidance for Industry: Human Gene Therapy for Hemophilia (July 2018) (CBER)
- Draft Guidance for Industry: Human Gene Therapy for Retinal Disorders (July 2018) (CBER)
- Draft Guidance for Industry: Human Gene Therapy for Rare Diseases (July 2018) (CBER)
- Q&A document for ICH S3A (May 2018) (CDER and CBER)
- Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations (August 2018) (CDER)

Cross-Agency Activities

FDA supports and encourages contributions to interagency and global efforts to assess alternative methods from the regulators' perspectives. Our experts across product centers in different disciplines have been actively participating in these initiatives.

- Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM): FDA representatives from each product center have participated in the joint effort to provide regulators' perspectives.
- Toxicology in the 21st Century (Tox21) Consortium: FDA center representatives participate in the Tox21 effort and provide regulators' input.
- **The U.S.-EU Nanotechnology Communities of Research (CORs):** The U.S.-European Union collaborated via conferences and meetings to understand the regulatory science needs and collaboratively develop standards needed in this field. NCTR's Dr. Anil Patri was the co-chair of the *11th European and Global Summit for Clinical Nanomedicine, Targeted Delivery and Precision Medicine − The Building Blocks to Personalized Medicine* (September 2018, 2018 European Foundation for Clinical Nanomedicine (CLINAM) in Basel, Switzerland).
- FDA developed a standard guide E3143 through the ASTM E56.02 Nanotechnology Subcommittee: *Practice of Performing Cryo-Transmission Electron Microscopy of Liposomes*: Standards developed for characterization and in vitro studies would help streamline the submission from industry. FDA's standards program is enabling collaborative development of standards, which is much needed in novel technologies and in vitro assessment. The final standard is published at ASTM.
  (NCTR and cross-center)
- Led by NCTR, three work items are proposed through ASTM E56.08 for evaluating nanomaterial that will enable the prediction of potential immunotoxicological effects (WK60373, WK60553, WK60554). In vitro methods developed through ASTM with stakeholder involvement can be used for predicting immunotoxicity of nanomaterials. These are identified through the Global Summit and internal FDA needs for nanomaterial assessment to help streamline submissions and minimize multiple iterations of submissions for review. It is a work in progress.
  (NCTR and via the cross-Center collaboration effort)

- New/ongoing submissions to CDRH of Medical Device Development Tools (MDDTs) for several in vitro alternative methods for different types of traditional animal-based biocompatibility testing
  (CDRH)
- Color Hazard and RISk calculator (CHRIS), submitted for Medical Device Development Tools (MDDT) pre-qualification package
  (CDRH)
- Toxicology Working Group (TWG) initiatives:
  - Set up TWG SharePoint (SP) Project and Scientific Event-Sharing System to share toxicology relevant scientific event information (seminars, webinars, workshops, training courses, etc.) within the Agency for our colleagues to efficiently access relevant information and participate in these activities.
  - Created TWG affiliates and Interest Group (IG) Project to broaden our toxicology community and encourage our experts' involvement in several specific toxicology topics such as immunotoxicity, liver toxicity, cardiotoxicity, neurotoxicity.
  - Started Toxicology Seminar Series (TSS) to raise stimulating toxicology-relevant topics to be shared within the Agency toxicology community. The goal is to train and educate our regulators and to enhance understanding of pros and cons of new technologies when introduced at the seminar.
- FDA experts have supported the Test Guidelines Program (TGP), Organization for Economic Cooperation and Development (OECD), by participating in the expert groups and providing experts' comments.
- NIH Tissue Chip Consortium: FDA representatives from each center have participated in the joint effort to provide regulators' perspectives.

Presentations

FDA experts were frequently invited to give presentations on topics related to alternative tools (e.g. context of use). These presentations enable FDA to share our thoughts, stimulate discussions, enhance mutual understanding, and promote further conversations on how new approaches can support FDA regulatory needs.

- Dr. Paul Brown presented:
  - *Regulatory Expectations on the Qualification of Alternative Assays for Regulatory Decision Making* at the Toxicology Forum 42nd Annual Winter Meeting (January 2018) (CDER)
  - *FDA's Predictive Toxicology Roadmap* at the Regulatory Science Workgroup (March 2018) (CDER)
- Presentation on the Roadmap session, the Toxicology Forum 44th Annual Summer Meeting (July 2018) (CDER, CDRH, CFSAN, OCS)
- Dr. Paul Brown and Dr. Phil Yeager presented and participated in the panel discussion on the Roadmap and implementing new approaches, American Society of Cellular and Computational Toxicology (CDER, CTP)
- Dr. Antonia Mattia gave a Roadmap-related talk entitled *FDA's Predictive Toxicology Roadmap: Where is CFSAN?* at the scientific meeting of the Center for Research on Ingredient Safety at Michigan State University, November 13, 2018.
- Dr. Shruti Kabadi participated as Co-Chair in a session entitled *Current Practices in Federal Agencies Using Computational Tools in Safety Science* at the Toxicology and Risk Assessment Conference (TRAC) 2018, Cincinnati, OH. At the session, she presented *Assessment of Computational Methods for Assessment of Food Additives*, highlighting the use of pharmacokinetic modeling.
- Dr. William Mattes presented on *Tools, not Toys: From Innovation to Regulatory Application* at the 3rd Annual PREDiCT: 3D Models summit. 3D tissue systems, including "organoids" and microphysiological systems (MPS) hold real promise for more faithfully re-creating *in vitro* tissue structure and function in vivo. However, the transition from

using these systems for research and screening to regulatory applications is complex. This talk used the biomarker qualification efforts over the past decade as an analogy. (August 2018) (NCTR)

- Dr. Donna Mendrick gave a presentation titled *Use of Chip Technologies: Perspectives from a Regulatory Agency* at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting. (November 2018) (NCTR)
- FDA participated in the organizing committee and spoke at Future Tox IV meeting *Predictive Developmental and Reproductive Toxicology for Healthy Children* (November 2018) (CFSAN, NCTR)
- Dr. Donna Mendrick gave a presentation titled *FDA Perspectives on Tissues-on-Chips* at the at Keystone Symposia on Organs- and Tissues-on Chips (April 2018) (NCTR)
- Dr. Donna Mendrick was session leader and Amy Rosenberg and Robert Ball were presenters at the Gordon Research Conference on *Contemporary Advances and Challenges in Drug Safety Assessment.* (June 2018) (NCTR, CDER)
- Dr. David Saylor gave the Keynote presentation *Exposure models in biomedical applications* at the Modeling and Experiments in Drug Delivery Systems workshop. (September 2018) (CDRH)
- Dr. Vaishnavi Chandrasekar presented *Exposure predictions for rapid risk assessment of phase-separated additives in medical device polymers* at the American Chemical Society annual meeting. (March 2018) (CDRH)
- Dr. Srin Nagaraja presented *The Impact of Surface Processing and Fatigue Testing on Nickel Release in Nitinol Stents* at the North American Corrosion Engineers (NACE) meeting. (April 2018) (CDRH)
- Jennifer Goode presented on *The FDA MDDT Program and Considerations for In Vitro Alternatives for Biocompatibility Tests* at the 7th Annual Meeting of the American Society for Cellular and Computational Toxicology. (September 2018) (CDRH)
- Jia Guo and Alan Hood presented *CDRH review perspective: Considerations for chemical characterization of medical devices* at the 2018 SOT annual meeting) (CDRH)

- Kelly Brant, Matthew Savidge, and Luis Valerio, Jr. presented *Use of Adverse Outcome Pathways to Inform Tobacco Product Research* at the Society for Research on Nicotine and Tobacco Annual Meeting (SRNT)), 2018.
- Luis Valerio, Jr, Pei-Hsuan Hung, and Matthew Savidge presented *Investigating the Mode of Action for DNA Damage by Flavors in ENDS Using In Vitro and In Silico Screening* at the 20th International Conference on *In Vitro* Toxicology (ESTIV2018)) (CTP), 2018.
- Dr. Suzanne Fitzpatrick acted as the co-chair of the Future Tox 4-Predictive Toxicology for Healthy Children, (November 2018) (CFSAN)
- Dr. Suzanne Fitzpatrick presented *Predictive Toxicology for Regulatory Decisions: Implementing New Approaches at FDA* at the American Society for Cellular and Computational Toxicology Annual meeting (September 2018) (CFSAN)
- Dr. Suzanne Fitzpatrick presented *FDA Predictive Toxicology Road Map: How We Got There* at the DOD Roadmap Meeting (August 2018) (CFSAN)
- Dr. Suzanne Fitzpatrick presented *FDA Predictive Toxicology Road Map* at the Toxicology Forum Meeting (July 2018) (CFSAN)
- Dr. Suzanne Fitzpatrick presented *FDA's Predictive Toxicology Road Map* at the 2018 CAAT Spring Board meeting (May 2018) (CFSAN)
- Dr. Suzanne Fitzpatrick presented *FDA's Predictive Toxicology Road Map* at the ICCVAM Public Forum (May 2018) (CFSAN)
- Dr. Suzanne Fitzpatrick presented *The What, When, and How of Using Data from Alternative Testing Methods in Chemical Safety Assessments* at the Society of Toxicology Annual meeting (March 2018) (CFSAN)
- Dr. Suzanne Fitzpatrick acted as Chair for a Roundtable Session *Is a Common Mechanism of Action Essential to Conduct a Cumulative Risk Assessment or Just Nice to Have?* at the Society of Toxicology Annual meeting (March 2018) (CFSAN)
- Dr. Suzanne Fitzpatrick presented *FDA Participation in Tox 21 Partnership including Determining the Predicative Ability of In Vitro Microphysiological Systems* at the Society of Toxicology Annual meeting (March 2018) (CFSAN)

- Dr. Suzanne Fitzpatrick presented *Organs on a Chip and FDA Predictive Toxicology Road Map* at the Society of Toxicology Annual meeting (March 2018) (CFSAN)

Publications

Presenting research work in peer-reviewed papers or poster sessions further demonstrates FDA's efforts toward implementing the *Predictive Toxicology Roadmap* through a variety of research projects, collaborations, and continued communication.

- International Pharmaceutical Regulators Programme (IPRP): Expectations for Biodistribution (BD) Assessments for Gene Therapy (GT) Products (2018). CBER Pharm/Tox colleagues contributed to the regulatory reflection paper.
- Genotoxicity Assessment of Nanomaterials: Recommendations on best practices, assays and methods. Toxicological Sciences 164: 391-416, 2018. (CDRH) This paper is a five-year group effort involving analysis of all relevant published data with international collaborations of experts. A new genotoxicity test battery for safety assessment of Nanomaterials (NMs) is presented.
- Kabadi SV, Fisher J, Aungst J, Rice P (2018). Internal exposure-based pharmacokinetic assessment of 6:2 fluorotelomer alcohol (FTOH) and its metabolites. Food Chem Toxicol, 112: 375-82. (CFSAN)
- Nakamura N, Sloper D, Del Valle P, Mendrick D. (2018) Potential biomarker(s) for *in vitro* testicular toxicity assessments using a mouse testis organ culture system (Poster presentation at Future Tox IV) (NCTR)
- Shi Q in a joint effort to publish a paper titled Comprehensive Analyses and Prioritization of Tox21 10K Chemicals Affecting Mitochondrial Function by in-Depth Mechanistic Studies Environ Health Perspect. 2018, 126(7):077010. (NCTR)
- Zhang J, Ren L, Yang X, White M, Greenhaw J, Harris T, Wu Q, Bryant M, Papoian T, Mattes W, Shi Q.(2018) Cytotoxicity of 34 FDA approved small-molecule kinase inhibitors in primary rat and human hepatocytes. Toxicol Lett. 2018 Jul;291:138-148. (NCTR, CDER, external collaboration)

- Huo JH, Lyn-Cook B, Stockbridge N, and Pang L (2018) Sex-related differences in drug-induced QT prolongation and Torsades de pointes: a new model system with human iPSC-CMs. Toxicol Sci. 167(2): 360-374. (NCTR, external collaboration)
- Blinova K, Dang QY, Millard D, Smith G, Pierson J, Guo L, Brock M, Lu HY, Kraushaar U, Zeng HY, Shi H, Zhang XY, Sawada K, Osada, Kanda Y, Sekino Y, Pang L, Stockbridge N, Strauss D, Gintant G. (2018) International Multisite Study of Human Induced Pluripotent Stem Cell Derived Cardiomyocytes for Drug Proarrhythmic Potential Assessment. Cell Rep. 24(13):3582-3592. (CDER, CDRH, NCTR, external collaboration)
- Cai C, Wei F, Shi Q, Yang X, Strauss DG, Stockbridge N, and Pang, L. Fatty Acid-Based Medium Promoted Metabolic Maturation of Human Induced Pluripotent Stem Cell–Derived Cardiomyocytes (Poster presentation at Circulation. 2018;138:A16287) (CDER, NCTR)
- Wei F, Cai C, Lyn-Cook B, and Pang, L. (2018) Sex Differences in Repolarization Reserve, a Possible Mechanism for Sex-Related Differences in Drug-Induced QT Prolongation and Torsades de Pointes (Poster presentation at the SPS 2018 annual meeting) (NCTR, external collaboration)
- Rosas-Hernandez H, Cuevas E, Lantz SM, Imam A, Sturdivant N, Balachandran K, Slikker W, Paule MG, Ali SF (Presenter) (2018) Neurovascular unit components on a chip as a model to study traumatic brain injury (Poster presentation at the XIV International Congress of Toxicology) (NCTR, external collaboration)
- Rosas-Hernandez H, Escudero-Lourdes C, Cuevas E, Lantz SM, Imam SZ, Sturdivant N, Balachandran K, Slikker Jr. W, Paule MG, Ali SF (2018) Characterization of High Speed and Biaxial Stretch as in Vitro Models of Traumatic Brain Injury on the Blood-Brain Barrier (Poster presentation at the 12th World Congress on Brain Injury) (NCTR, external collaboration)
- Rosas-Hernandez H, Cuevas E, Escudero-Lourdes C, Lantz SM, Gomez-Crisostomo NP, Sturdivant NM, Balachandran K, Imam SM, Slikker Jr. W, Paule MP, Ali SF (2018)

Characterization of Biaxial Stretch as an I*n Vitro* Model of Traumatic Brain Injury to the Blood-Brain Barrier. Mol. Bio. 55(1):258-266. (NCTR, external collaboration)

- Rosas-Hernandez H, Cuevas E, Escudero-Lourdes C, Lantz SM, Sturdivant NM, Imam SZ, Sarkar S, Slikker W, Paule MG, Balachandran K, Ali SF (2018) Characterization of uniaxial high-speed stretch as an *in vitro* model of mild traumatic brain injury on the blood-brain barrier. Neurosci. Lett. 672: 123-129. (NCTR, external collaboration)
- Saylor DM, Craven BA, Chandrasekar V, Simon DD, Brown RP, Sussman EM (2018) Predicting patient exposure to nickel released from cardiovascular devices using multi-scale modeling. Acta Biomater. 70:304-314 (CDRH)
- Chandrasekar V, Janes DW, Saylor DM, Hood A, Bajaj A, Duncan TV, Zheng J, Isayeva IS, Forrey C, Casey BJ (2018) Conservative Exposure Predictions for Rapid Risk Assessment of Phase-Separated Additives in Medical Device Polymers. Ann Biomed. Eng. 46(1):14-24. (CDRH)
- Sussman E (2018) Determining Worst-Case Ni Release in Benchtop Studies of Nitinol (Poster presentation at the Society for Biomaterials annual meeting) (CDRH)
- Savery LC, Chandrasekar V, Saylor DM, Hood AM, Brown RP (2018) Safety assessment of color additives released from medical devices (Poster presentation at the 2018 SOT annual meeting) (CDRH)
- Skoog S, Guo J, Malinauskas R, Lu Q, Casey B. (2018) In Vitro Hemocompatibility Testing of Polymer Degradants from Medical Device Materials (Poster presentation at the 2018 SOT annual meeting) (CDRH)
- Guo J, Ghosh M, Peng G, Skoog S, Brown R (2018) Evaluation of Sample Preparation Methods in the ISO 10993-12 Standard: Challenges Associated with Exhaustive Extraction of Polymeric Materials for Biological Evaluation (Poster presentation at the 2018 SOT annual meeting) (CDRH)
- Skoog S et al., (2018) Round robin study to evaluate the reconstructed human epidermis (RhE) model as an *in vitro* skin irritation test for detection of irritant activity in medical device extracts. 50:439-449. (CDRH, external collaboration)

- ICCVAM Online Publication "A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States" (2018) (FDA cross-center colleagues co-authored the paper)
- Saylor D, Buehler B, Brown R, Malinauskas R (2018) Predicting Plasma Free Hemoglobin Levels in Patients Due to Medical Device-Related Hemolysis. ASAIO J 64 (Suppl. 1):3. It was also presented at the ASAIO 2018 Annual Conference in June 2018. (CDRH, CBER)
- Craven B, Aycock K, Herbertson L, Malinauskas R (2018) A surrogate modeling approach to predict device-specific hemolysis power law coefficients in blood-contacting medical devices. ASAIO J 64 (Suppl. 1):14. It was also presented at the ASAIO 2018 Annual Conference in June 2018. (CDRH, external collaboration)
- Jamiolkowski M, Lu Q, Malinauskas R (2018) Effects of Animal Blood Type on *In Vitro* Dynamic Thrombogenicity Tests of Biomaterials. ASAIO J 64 (Suppl. 1):79. It was also presented at the ASAIO 2018 Annual Conference in June 2018. (CDRH, external collaboration)
- Herbertson L, Shin S, D'Souza G, Rezvan P, Drummond A, Retta S, Hahn J, Rinaldi J (2018) Development of Mock Circulatory Loops to Assess VAD Performance. ASAIO J 64 (Suppl. 1):81. It was also presented at the ASAIO 2018 Annual Conference in June 2018. (CDRH, external collaboration)
- Hariharan P, Aycock K, Buesen M, Day S, Good B, Herbertson L, Steinseifer U, Manning K, Craven B, Malinauskas R (2018) Inter-Laboratory Characterization of the Velocity Field in the FDA Blood Pump Model Using Particle Image Velocimetry (PIV). ASAIO J 64 (Suppl. 1):82. It was also presented at the ASAIO 2018 Annual Conference in June 2018. (CDRH, external collaboration)
- Baek J, Yalamanoglu A, Brown R, Malinauskas R, Buehler P (2018) Renal Toxicodynamic Effects of Extracellular Hemoglobin After Acute Exposure Toxicol Sci. 166(1):180-191. (CDRH, CBER)

- Smirnova L, Kleinstreuer N, Corvi R, Levchenko A, Fitzpatrick SC, Hartung T (2018) 3S - Systematic, systemic, and systems biology and toxicology ALTEX. 35(2):139-162. (CFSAN, external collaboration)
- Marshall LJ, Austin CP, Casey W, Fitzpatrick SC, Willett C (2018) Recommendations toward a human pathway-based approach to disease research. Drug Discov Today 23(11):1824-1832. (CFSAN, external collaboration)
- Thomas RS, Paules RS, Simeonov A, Fitzpatrick SC, Crofton KM, Casey WM, Mendrick DL (2018) The US Federal Tox21 Program: A strategic and operational plan for continued leadership. ALTEX. 2018 Mar 8;35(2):163-168. (CFSAN, external collaboration)
- Strickland J, Clippinger AJ, Brown J, Allen D, Jacobs A, Matheson J, Lowit A, Reinke EN, Johnson MS, Quinn MJ Jr., Mattie D, Fitzpatrick SC, Ahir S, Kleinstreuer N, Casey W. (2018) Status of acute systemic toxicity testing requirements and data uses by U.S. regulatory agencies. Regul Toxicol Pharmacol. 94:183-196 (CFSAN, external collaboration)

Conclusion

Through the scientific activities described above, FDA is actively collaborating with our domestic and international stakeholders to understand the new technologies and their application to our regulatory mission. In this regard, FDA is holding a public workshop on Wednesday, September 18, 2019 to highlight the work we have been doing to support and implement FDA's Predictive Toxicology Roadmap.