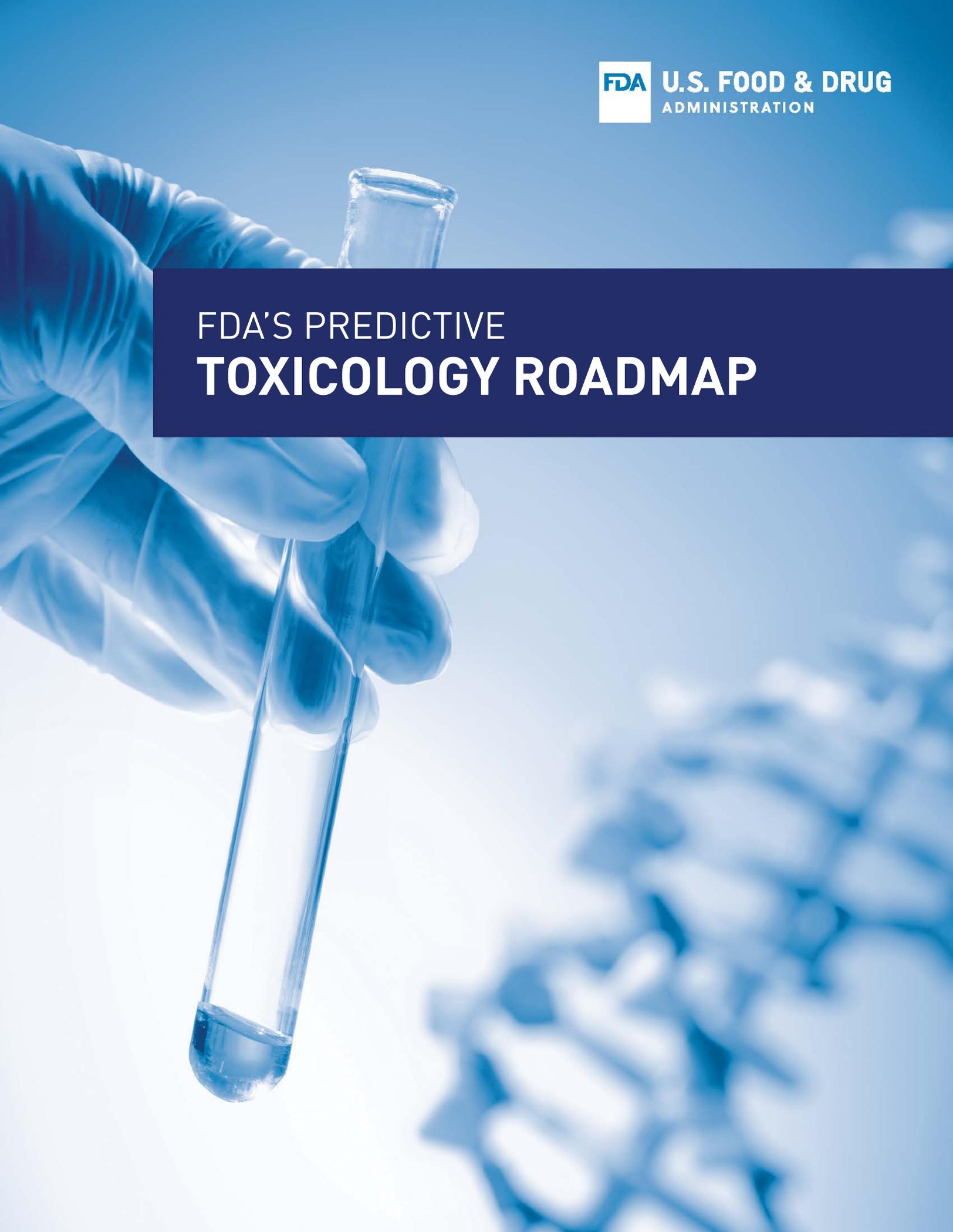




U.S. FOOD & DRUG
ADMINISTRATION

A hand wearing a white latex glove holds a clear glass test tube containing a small amount of blue liquid. The background is a soft-focus blue scene with several white, star-shaped pills scattered on a surface.

FDA'S PREDICTIVE
TOXICOLOGY ROADMAP





Executive Summary

The cumulative effects of globalization, rapidly evolving technologies, and emerging areas of science have created unprecedented opportunities and challenges for the U.S. Food and Drug Administration (FDA). For example, breakthroughs in many areas of science are generating new tools and methods that are being incorporated into the *science of toxicology*.

During the past decade, FDA scientists have taken significant steps to upgrade their toxicology toolboxes. However, a comprehensive strategy is needed to evaluate new methodologies and technologies for their potential to expand FDA's toxicology predictive capabilities and to potentially reduce the use of animal testing. Acceptance of any new toxicology methods will require sufficient convincing data as well as continuous dialogue and feedback among all relevant stakeholders from development to implementation, including qualification and acceptance by regulatory authorities.

To ensure that FDA continues to employ cutting-edge science to assess the safety and effectiveness of its regulated products and to leverage advances being made in toxicology, the FDA Commissioner tasked the Agency's Toxicology Working Group with developing a roadmap for integrating predictive toxicology methods into safety and risk assessments.

The Toxicology Working Group recommends a six-part roadmap for achieving identified goals. The roadmap is summarized below and presented in more detail in the document that follows.

Part One: Organizing Committee

FDA has formed a senior-level Toxicology Working Group to (1) foster enhanced communication among FDA product centers and researchers and (2) leverage FDA resources to advance the integration of emerging predictive toxicology methods and new technologies into regulatory safety and risk assessments. Specific activities will help identify areas where research is needed and may reduce duplication of efforts inside and outside FDA.

Part Three: Continued Communication

FDA will continue to reaffirm its commitment to and support for incorporating data from newly qualified toxicology methods into regulatory submissions and that it encourages discussions with stakeholders as part of the regulatory submission process. FDA product centers will encourage sponsors to submit a scientifically valid approach for using a new method early in the regulatory process and to engage in frequent communication with the Agency. Such interactions are essential to ultimately ensuring that new toxicology methods can be used in regulatory risk assessments.



Part Two: Training

Continuing ongoing education in new predictive toxicology methods is essential for FDA regulators. Among other steps, FDA's Toxicology Working Group has established an Agency-wide education calendar of events and a Toxicology Seminar Series to introduce concepts of new toxicology methodologies and updates in toxicology-related topics.

Part Five: Research

FDA's research programs will identify data gaps and support intramural and extramural research to ensure that the most promising technologies are identified, developed, validated, and integrated into the product pipeline.

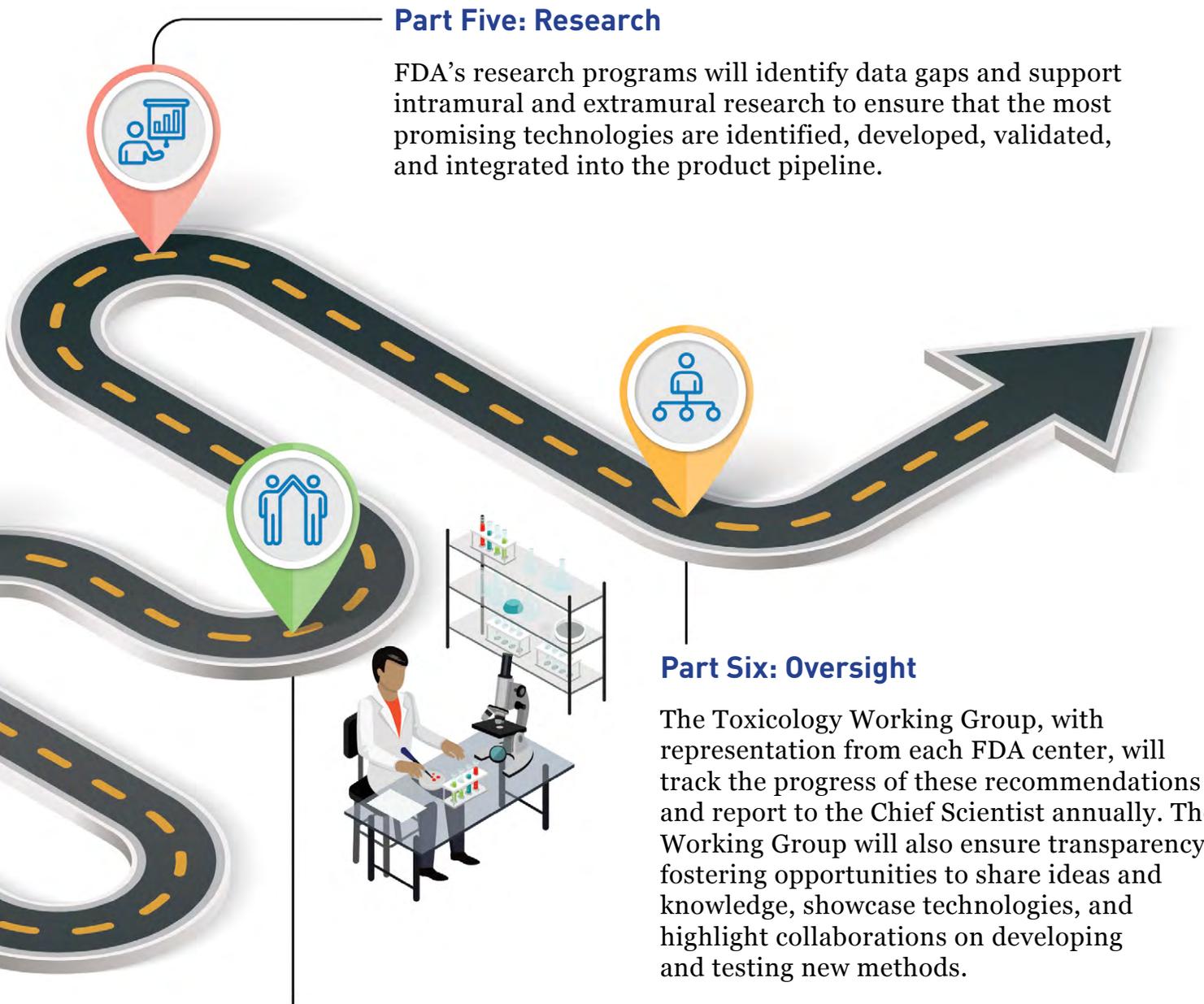
Part Six: Oversight

The Toxicology Working Group, with representation from each FDA center, will track the progress of these recommendations and report to the Chief Scientist annually. The Working Group will also ensure transparency, fostering opportunities to share ideas and knowledge, showcase technologies, and highlight collaborations on developing and testing new methods.

This six-part roadmap, described in more detail in the document that follows, identifies FDA's critical priority areas for energizing a new and enhanced FDA engagement in transforming the development, qualification, and integration of new toxicology methodologies and technologies into regulatory application. FDA believes that successfully implementing the roadmap and engaging with diverse stakeholders will enable it to fulfill its regulatory mission today while preparing for the challenges of tomorrow.

Part Four: Collaborations

FDA will continue its long practice of fostering collaborations across sectors and disciplines nationally and internationally. FDA considers these types of partnerships pivotal to identifying the needs, maintaining momentum, and establishing a community to support delivery of new predictive toxicology methods.



Introduction

The impacts of globalization, rapidly evolving technologies, and emerging areas of science have created unprecedented challenges and opportunities for the U.S. Food and Drug Administration (FDA). These impacts underscore the criticality of ensuring that FDA continues to employ cutting-edge science to assess the safety and effectiveness of its regulated products. Strong science underpins everything FDA does. Therefore, keeping pace with advances in basic and applied science and technology is crucial to the Agency's ability to reach sound regulatory decisions and retain the public's trust.

The scientific discipline of toxicology is particularly essential to FDA's mission because it is applied across the breadth of FDA-regulated product areas. Toxicological testing is performed during the development and evaluation of FDA-regulated products, ranging from human and animal drugs, to medical devices, to food and food ingredients, to human biologics to tobacco products.

Breakthroughs in many areas of science are generating new tools and methods that are being incorporated into the *science of toxicology*. Advances in systems biology, stem cells, engineered tissues, and mathematical modeling are creating unique opportunities to improve toxicology's predictive ability, potentially enhancing our ability to predict risk. These advances are expected to help bring medical products to market faster or prevent products with increased toxicological risk, including new tobacco products, from reaching the market. Also critical is the potential of these advances for replacing, reducing, and/or refining animal testing.

FDA toxicologists across the Agency have extensive experience using available tools to make tough scientific decisions about the safety and effectiveness of the products they regulate. These toxicologists have seen what works and what does not; they can provide critical insights and help solve challenges in defining how best to create and evaluate the new tools being developed to predict and assess the potential toxicity of FDA-regulated products.

FDA product centers have taken significant steps to upgrade their toolboxes. However, challenges remain in coordinating the use of new methodologies and technologies. For example, FDA's six product centers have very different legal authorities for evaluating product safety or toxicity. Nevertheless, greater cross-center collaboration can help accelerate the use of emerging predictive toxicology methods in various programs and in the regulatory arena. This can be achieved by leveraging skills, abilities, and resources in each of FDA's centers to analyze the impediments to acceptance of new methods and develop strategies to overcome them.

FDA recognizes that a comprehensive strategy is needed to evaluate new methodologies and technologies for their potential to offer greater predictive ability. Examples of areas where new evaluation approaches could be especially useful include helping to identify the potential risks related to chronic and low-dose exposures to the substances and substance mixtures that make up the products FDA regulates.

A Vision for the Future of Toxicity Testing

Efforts to improve our ability to predict toxicological risk have a long history. For example, in 2007, as part of a concerted effort to improve toxicity testing methods for the entire scientific community, the National Research Council (NRC) of the U.S. National Academy of Sciences issued a report titled *Toxicity Testing in the 21st Century: A Vision and a Strategy (Tox21)*. The Tox21 report outlined a new vision for the future of toxicity testing, advocating a shift away from traditional animal studies, which can be expensive and time consuming and have drawbacks, toward a focus on alternative methods that evaluate the effects of chemicals on biological processes. In 2017, NRC issued a follow-up report, sponsored in part by FDA, titled *Using 21st Century Science to Improve Risk-Related Evaluations*.

In its 2010 Advancing Regulatory Science Plan, FDA identified transforming toxicology as a key scientific priority for the Agency where collaborative scientific research is essential and offers enormous opportunities. The Plan promoted developing a better understanding of toxicity mechanisms by evaluating safety and risk assessment data at multiple biological levels, including genes, proteins, biochemical pathways, and cell/organ function.

Transforming toxicology remains a key priority for FDA. Having taken significant steps towards integrating new predictive technologies into the toxicology programs of its different product centers, FDA now proposes coordinating all FDA initiatives into a focused roadmap, an FDA Predictive Toxicology Roadmap, for advancing predictive toxicology in regulatory risk assessments.



Charge to the FDA Toxicology Working Group

To this end, the FDA Commissioner tasked FDA's Toxicology Working Group with development of a roadmap for integrating emerging predictive toxicology methods and new technologies into regulatory safety and risk assessments. Composed of senior toxicologists from FDA's different product centers and its National Center for Toxicological Research, the Working Group has deep expertise in each FDA product area and knowledge of the legal authorities for evaluating safety and toxicity in that product area. In developing the roadmap, the Working Group relied heavily on the recommendations in the NRC's two reports, Tox21 and the 2017 follow-on report. The Working Group is well-positioned to serve as a catalyst for transforming toxicology at FDA.

Roadmap Goals

The key goal of the roadmap is to invigorate and strengthen FDA's long commitment to promoting the development and use of new technologies to better predict human, animal, and environmental responses to a wide range of substances relevant to FDA's regulatory mission.

This roadmap will address needs and opportunities that typically extend across FDA's product centers and product areas. It will present current FDA thought on viable ways to:

- foster the development and evaluation of emerging toxicological methods and new technologies and
- incorporate these methods and technologies into regulatory review, as applicable.



Context of Use

Critical to FDA's ability to reach sound regulatory decisions and to retain the public's trust are high-quality data; a thorough, unbiased, and transparent scientific review process; and confidence in the tools used to demonstrate safety and assess risk. FDA must be able to evaluate the applicability, limitations, relevance, reliability, reproducibility, and sensitivity of a test or series of tests (performance standards) to confirm that the test or series of tests has been appropriately *validated* or *qualified*. Current formal approaches to validation involve lengthy and expensive processes that may not be necessary for all uses of a particular test.

Rather than validation, an approach we frequently take for biological (and toxicological) models and assays is *qualification*. Within the stated *context of use*, qualification is a conclusion that the results of an assessment using the model or assay can be relied on to have a specific interpretation and application in product development and regulatory decision-making.

The *context of use* refers to a clearly articulated description delineating the manner and purpose of use for the tool (when and how it will be used). Adequately specifying the context of use is often a difficult first step towards qualification and regulatory acceptance of new methodologies. Qualification also identifies the boundaries of the available data that adequately justify the use of the tool. Models and assays should be suited for a purpose and, in that context, they will have different applicability, assumptions, and limitations.

Once a new model or assay is considered qualified by FDA for a specific context of use, industry and other stakeholders can use it for the qualified purpose during product development, and FDA reviewers can be confident in applying it without needing to re-review the underlying supporting data.



Toxicology Issues that Need Addressing for FDA-Regulated Products

Identifying FDA's toxicology needs is an important initial exercise in forming a roadmap for integrating emerging predictive toxicology methods and new technologies into regulatory safety and risk assessments. New approaches should focus on providing the information FDA needs to make sound, science-based regulatory decisions. Some of the ways toxicology information is used in FDA's regulation of products include the following.

- Identifying dose levels or systemic exposures at which no adverse effects are observed
- Identifying potential target organs of toxicity
- Identifying potential developmental and reproductive toxicity
- Identifying potential carcinogenicity
- Determining a reasonably safe first-in-human dose for human pharmaceuticals
- Determining an acceptable human dietary exposure for hazards in foods (including food additives, veterinary drug residues, and contaminants)
- Identifying and understanding the factors that affect different responses by sub-populations
- Determining comparative toxicity of tobacco products, which are inherently toxic
- Determining possible local tissue responses to an implanted medical device

Toxicology Areas That Could Benefit from Improved Predictivity

Certain areas of toxicology prediction remain challenging and could benefit from greater predictivity. In addition, often a better understanding of mechanisms can be useful when considering the possible human relevance of toxicological findings. Some of the areas that could benefit from improvement include the following.

- Identifying rare (“idiosyncratic”) toxicities
- Characterizing potential non-genotoxic carcinogens
- Understanding chemical transport into sensitive biological compartments (e.g., brain, fetus)
- Identifying human relevance of toxicity findings, including developmental and carcinogenicity findings
- Modeling to support decision-making in cases of data gaps
- Optimizing in vitro alternative methods for use with low dose mixtures extracted from medical devices or with aqueous and non-aqueous lubricants used as medical devices or accessories
- Understanding how Adverse Outcome Pathways (AOPs) can reduce uncertainty in identifying hazards and assessing risk

Promising New Technologies in Predictive Toxicology

New approaches are being explored in many scientific disciplines that may be relevant to toxicology. These methods span the technical spectrum, from computational methods and simple and complex in vitro systems to innovative animal models, such as humanized animals or genetically altered organisms, and many others. This roadmap cannot catalog or prioritize these vast and dynamic fields of research. However, many of these approaches might be able to address some of the needs and gaps identified, although it is not possible to predict which ones will be most successful. Each approach requires evaluation for its usefulness within a context of use-specific manner as discussed above.

Over the years, FDA has been a critical participant in developing and adopting new technologies. The experience gained from these efforts continues to inform activities, including international activities, around a number of toxicology-related areas.

Microphysiological systems like tissues or organs on a chip

FDA participates in the Defense Advanced Research Projects Agency (DARPA)¹ and National Center for Advancing Translational Sciences (NCATS)² programs, and it is initiating internal research programs with such systems. FDA's Center for Food Safety and Nutrition has entered into a Cooperative Research and Development Agreement to bring organs on a chip technology into FDA laboratories.

Alternative test methods for reproductive toxicity testing

FDA's Center for Drug Evaluation and Research is working through the International Conference on Harmonisation (ICH) to consider the regulatory use of alternative test methods for reproductive toxicity testing, as outlined in the Step 2 draft guidance ICH S5(R3) available at www.ich.org.

Computational toxicology

FDA's research programs contribute to updating existing and developing new quantitative structure–activity relationship (QSAR) programs and to devising new computational approaches.

In vitro alternatives

FDA participates in the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which is evaluating non-animal methods for assessing a variety of endpoints.

Quantitative risk assessment (QRA) addressing the complex chemical mixtures of tobacco products

FDA's Center for Tobacco Products conducted a two-day workshop on risk assessment and has been providing feedback to industry on QRAs submitted with product applications.

Read across methodology

This methodology uses data from a data-rich substance for a data-poor substance that is considered similar enough to use the same data as a basis for assessing safety. FDA participates in an ICCVAM Work Group on this area.

¹ The Defense Advanced Research Projects Agency (DARPA) is an agency of the United States Department of Defense responsible for the development of emerging technologies for use by the military. See DARPA website <https://www.darpa.mil/>

² <https://ncats.nih.gov/>

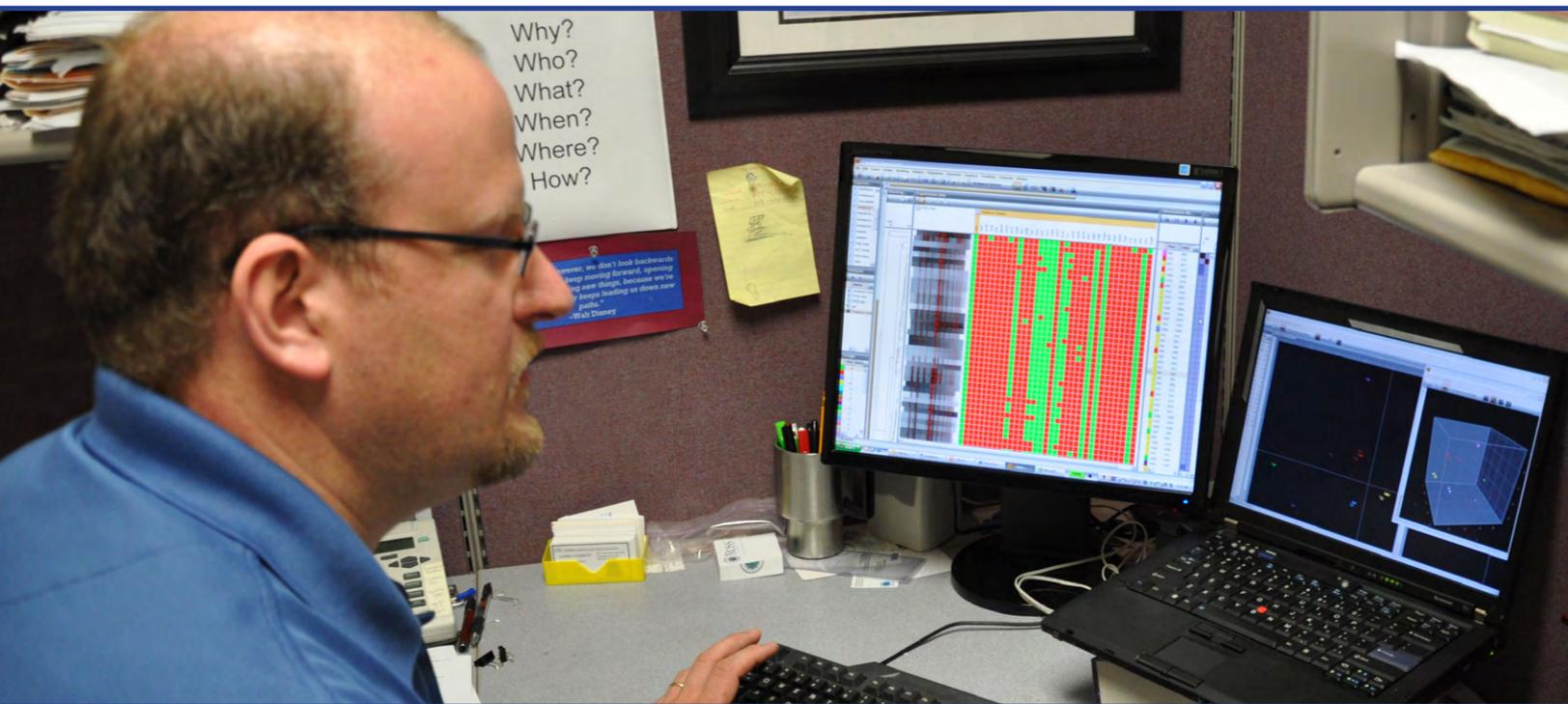
FDA's Proposed Predictive Toxicology Roadmap

Each of FDA's six product centers has very different legal authorities for evaluating product safety or toxicity. Statutes allow FDA to require the submission of extensive safety or toxicity data in some product areas, while FDA's authority to require information in other product areas is limited. The context of use can be significantly different for different product areas. Therefore, implementing newer and/or alternative tools may also be different across product areas. Nevertheless, despite these differences, FDA toxicologists from across the Agency share many concerns.

Tools that provide insight into the toxicological endpoints and toxicological pathways for select, generally well-characterized components of FDA-regulated products are of particular value to FDA. This is because FDA-regulated products often include complex mixtures that can be an exception to the single-moiety approach. These products benefit from in-depth toxicological evaluations for ingredients and constituents.

The key critical questions that need to be addressed by toxicology data are invariably those that characterize the potential toxicity of an FDA-regulated product on human consumers, patients, and animals. As FDA moves to accept newer models, whether *in vitro*, *in silico*, *ex vivo*, or *in vivo*, there is a critical need to determine the degree of concordance between the data obtained from the model and toxicity to humans or animals.

Acceptance of any new toxicology methods will require sufficient convincing data so that regulators and the scientific community are confident in the suitability of the new method. Acceptance of alternative methods requires continuous dialogue and feedback between all partners from development to implementation, including qualification and acceptance by regulatory authorities.



A Six-Part Framework for New or Enhanced FDA Engagement in the Science of Toxicology

FDA's Working Group recommends a six-part framework for new or enhanced FDA engagement in the science of toxicology.

1. Organizing Committee

FDA has formed a senior-level Toxicology Working Group to (1) foster enhanced communication among FDA product centers and researchers and (2) leverage FDA resources to advance the integration of emerging predictive toxicology methods and new technologies into regulatory safety and risk assessments.



Working Group activities include:

- discussions around and review of ongoing FDA research;
- access to internal databases to leverage data and identify gaps in the current testing paradigms, where newer methods are critical to mitigate uncertainty;
- development of context of use examples; and
- acceptance of newer toxicology methods (e.g., criteria for incorporating more predictive models in regulatory risk assessment).

These activities will help identify areas where research is needed and may reduce duplication of efforts inside and outside FDA.

2. Training

Continuing ongoing education in new predictive toxicology methods is essential for FDA regulators. To this end, FDA's Toxicology Working Group has established an Agency-wide education calendar of events and a Toxicology Seminar Series to introduce concepts of new toxicology methodologies and updates in toxicology-related topics.



Developing and maintaining a cutting-edge capacity in this complex field touches on a broad range of skills. FDA will work to ensure that a wide range of disciplines, expertise, and individuals are engaged in developing or adopting appropriate predictive toxicology methods and technologies. Additionally, FDA will continue to make training in new test methods available during the development process so that regulators understand the basis of these methodologies before they are integrated into regulatory application.



3. Continued Communication

FDA will continue to reaffirm its commitment to and support for incorporating data from newly qualified toxicology methods into regulatory submissions and that it encourages discussions with stakeholders as part of the regulatory submission process. FDA product centers will encourage sponsors to submit a scientifically valid approach for using a new method early in the regulatory process and to engage in frequent communication with the Agency. Such interactions are essential to ultimately ensuring that new toxicology methods can be used in regulatory risk assessments.



4. Collaborations

FDA will continue its long practice of fostering collaborations across sectors and disciplines nationally and internationally. An example is the DARPA/FDA/NCATS Partnership that was formed to develop in vitro microphysiological systems, also known as organs on a chip. FDA considers these types of partnerships pivotal to identifying the needs, maintaining momentum, and establishing a community to support delivery of new predictive toxicology methods.



5. Research

FDA's research programs will identify data gaps, such as understanding the concordance between animal and human responses (i.e., biomarkers of toxicity) and understanding how the performance of these markers and their interpretation may vary across different organ systems and species and within human populations (i.e., precision medicine). FDA supports intramural and extramural research to ensure that the most promising technologies are identified, developed, validated, and integrated into the product pipeline.



6. Oversight

The Toxicology Working Group, with representation from each FDA center, will track the progress of these recommendations and report to the Chief Scientist annually. Its key goals are to ensure continued communication and collaboration among the different FDA centers and with the Agency's stakeholders. The Working Group will help foster collaborations within the Agency, nationally, and internationally and will be pivotal to maintaining momentum for the roadmap goals. The Working Group will also ensure transparency, fostering opportunities to share ideas and knowledge, showcase technologies, and highlight collaborations on developing and testing new methods.

Conclusion

This six-part roadmap identifies the critical priority activities for energizing new or enhanced FDA engagement in transforming the development, qualification, and integration of new toxicology methodologies and technologies into regulatory application. FDA's Toxicology Working Group is committed to helping achieve the success of this roadmap. Implementing the roadmap and engaging with diverse stakeholders will enable FDA to fulfill its regulatory mission today while preparing for the challenges of tomorrow.



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