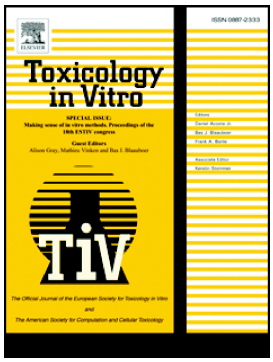

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Predictive Toxicology for Regulatory Decisions: Implementing New Approaches at US Food and Drug Administration

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Introduction

In 2007, the National Academy of Sciences published a report entitled "Toxicity Testing in the 21st Century- A Vision and Strategy". This report was sponsored and funded primarily by the US Environmental Protection Agency. The report envisioned the use of cell- based high throughput assays to understand how chemicals perturb normal cellular pathways (i.e. toxicity pathways) in lieu of extensive animal testing. It also endorsed *in vitro* to *in vivo* extrapolation methods that would integrate results to predict hazard/risk. This would allow broader coverage of chemicals & endpoints in addition to reducing the cost & time of testing while using fewer animals.

Although this report was one of the tipping points for greater focus on new ways to conduct toxicology testing, to a large extent the recommendations were applicable to regulatory agencies that oversaw large numbers of chemicals with very little safety data available. This is not the case for the Food and Drug Administration (FDA).

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.

FDA Needs for Predictive Toxicology

The needs of regulatory toxicologists are very different than for research toxicologists. Regulators must assure their toxicology toolbox keeps pace with advances in science and technology. But regulators must also decide how much evidence is sufficient to determine that a new tool is qualified to make safety decisions that potentially affect millions of consumers. It is a delicate balance between assuring safety and impeding innovation. And one that is often not fully appreciated by new method developers.

FDA recognizes that a comprehensive strategy is needed to evaluate new methodologies and technologies for their potential to offer greater predictive ability. Any successful federal agency roadmap needs to build upon the successful and perhaps unsuccessful previous activities of that agency. FDA realized that fostering collaborations between government researchers and regulators and between government regulators, industry, stakeholders and academia will help bridge the gap between regulators and researchers and ensure the most promising technologies are identified, developed, evaluated and integrated into regulatory risk assessment.

FDA's experience with existing partnerships helped build a strong foundation for FDA's understanding of what should be included in its Predictive Toxicology Roadmap. One example was the FDA Critical Path Predictive Safety Testing Consortium. FDA and the European Medicines Agency engaged in a collaborative data sharing and testing effort with academia and industry, spearheaded through the Critical Path Institute. This successful collaboration resulted in qualification of several non-clinical biomarkers of toxicity.

FDA also realized the importance of training regulators early and often in emerging methods and methodologies. One example was the Memorandum of Understanding with Society of Toxicology (SOT) for joint training in toxicology. The partnership lead to SOT and FDA to jointly developing workshops on cutting-edge, future-oriented toxicological science. These workshops are open to scientists worldwide and often result in 400 or more participants from over 17 different countries. These workshops provide an avenue of discussion for FDA and outside scientists on a wide variety of emerging technologies.

Another example of an important and informative partnership is the FDA-Defense Advanced Research projects Agency (DARPA)-National Institutes of Health (NIH) Microphysiological Systems Program started in 2011 to support the development of human microsystems, or organ "chips," to screen for safe and effective drugs swiftly and efficiently before human testing programs. This was a unique partnership because it involved regulatory scientists at the very beginning to address identified gaps in knowledge needed to regulate FDA products.

Formation of an FDA Predictive Toxicology Roadmap Committee

In 2015 FDA formed an FDA Senior Toxicologist Working Group that consisted of Senior Toxicologists from all six FDA program offices plus the National Center for Toxicology Research (NCTR) and the Office of the Commissioner. The purpose was to share information on new toxicology methods and to familiarize FDA regulatory and research scientists on emerging

toxicology tests and their usefulness in risk assessment. 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.

Although each of FDA's product centers has very different legal authorities for evaluation of product safety, FDA toxicologists agreed that greater cross-center collaboration would help accelerate the use of emerging predictive toxicology methods. A subgroup of the FDA Toxicology Workgroup, with members from multiple centers and offices of FDA, was formed to reach consensus on the common needs and important elements to be included in the Roadmap.

The overall goal of the roadmap was to energize new or enhanced FDA engagement in transforming the development, qualification, and integration of new toxicology methodologies and technologies into regulatory applications. Engaging diverse stakeholders would enable FDA to better fulfill its regulatory mission today while preparing for the challenges of tomorrow.

FDA emphasizes the concepts of Qualification and Context of Use in its roadmap. 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. Context of use refers to a clearly articulated description delineating the manner and purpose of use for the tool.

FDA recognized that including regulators up front in new method development would help to expedite acceptance of new methods for regulatory use. New toxicology methods were tools to answer regulatory questions. Regulators need to delineate what tools are needed to answer these questions. Additionally, regulators need to identify gaps for additional research.

Once decisions were made on the content of the roadmap, the group needed a framework to incorporate all these elements/ideas into one document. The chair of the committee wrote a draft of the roadmap, incorporating all these ideas. This was reviewed and revised by the Roadmap Committee, approved and sent to the Office of the Commissioner for adoption. One important element was that accountability was built into the roadmap. Each program office must report its activities to the Office of the Commissioner on a yearly basis.

Elements of the FDA Predictive Toxicology Roadmap

The FDA Predictive Toxicology Roadmap was Announced December 6, 2017. https://www.fda.gov/science-research/about-science-research-fda/fdas-predictive-toxicology-roadmap. The roadmap has six important elements and the activities under each element described below:

1. FDA Senior Level Toxicology Working Group
    - 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).

2. Training
    - Training of FDA regulators and researchers.
    - Continuing ongoing education in new predictive toxicology methods is essential for FDA regulators.
    - 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.
3. Continued Communication
    - Reaffirm FDA's commitment to incorporate data from newly qualified toxicology methods into regulatory missions.
    - Encourage discussions with stakeholders as part of the regulatory submission process.
    - Encourage sponsors to submit a scientifically valid approach for using a new method early in the regulatory process.
4. Collaborations with Stakeholders
    - Foster collaborations across sectors and disciplines nationally and internationally.
    - Pivotal to identifying the needs, maintaining momentum, and establishing a community to support delivery of new predictive toxicology methods.
5. Leveraging 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.
6. Oversight by Office of the Commissioner
    - Track the progress of these recommendations and report to the FDA Chief Scientist annually.
    - Ensure transparency, fostering opportunities to share ideas and knowledge, showcase technologies, and highlight collaborations on developing and testing new methods.

Results of the 2018 Public Meeting on FDA's Predicative Toxicology Roadmap

FDA held a public hearing on Wednesday, September 12, 2018 to solicit comments on how to foster the development and evaluation of emerging toxicological methods and new technologies and incorporate them into regulatory review, as applicable. At the Public meeting, FDA heard the following comments:

- *FDA should make public the Annual reports by the FDA centers on activities that advanced predictive toxicology.* FDA agreed and make the first report to the Office of the Commissioner public. This report includes activities from all FDA Offices and can be found at https://www.fda.gov/media/128045/download
- *FDA should do a better job communicating with stakeholder to encourage discussion on the use of qualified new toxicology methods early in the regulatory process*. FDA agreed and is holding a second public meeting on some of the activities discussed in the roadmap to give our stakeholder an opportunity to discuss these activities further with FDA. More information can be found at https://www.fda.gov/science-research/about-science-research-fda/implementing-fdas-predictive-toxicology-roadmap-update-fda-activities-09182019-09182019

Overall, participants in the public meeting strongly endorsed the Predictive Toxicology Roadmap goals. FDA will continue to update its stakeholders on its predictive toxicology activities through the Predictive Toxicology website on www.fda.gov.

Conclusion

In conclusion,the six-part FDA Predictive Toxicology 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 applications. FDA is fully committed to achieving 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.

Highlights

FDA needs for Predictive Toxicology

FDA Predictive Toxicology Roadmap

Qualification of New In Vitro Methods

Importance of Working with Stakeholders in Advancing New Methods

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.