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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

COMMENTARY

Advancing Regulatory Science Through Innovation: In Vitro Microphysiological Systems

The challenge of modern product development and globalization underscores the critical importance of ensuring that regulatory science keeps pace with advances in basic and applied science and technology. In 2011, the US Food and Drug Administration (FDA) launched its Advancing Regulatory Science Initiative to accelerate scientific innovation and improve regulatory decision-making practices, with the goal of providing safe and effective products. The FDA identified several priority areas in which the Agency believed that new or enhanced engagement was essential in fulfilling its public health and regulatory mission. The priority areas identified are considered cross-cutting and are believed to address the needs of multiple product areas. Success in regulatory science activities in the identified areas "will enhance product development, evaluation and health outcomes related to multiple products and populations."[1]

One priority area identified was modernizing toxicology. It is the intent that the identification and adaption for regulatory use of modern toxicological tools will improve preclinical safety predictions. Specific areas of focus included developing better models of human adverse response, identifying and evaluating more reliable biomarkers for monitoring toxicities, and using computational tools and in silico modeling to draw conclusions from a wide range of preclinical safety data types and sources. Taken together, these predictive models would create a new vision for the future of toxicity testing that relied less on animal studies and instead focused on in vitro methods that would evaluate the effects of chemicals on biological processes using cells, cell lines, or cellular components, preferably of human origin.

Critical to the FDA's ability to reach sound 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 that it uses to show safety or assess risk. Taken together, these factors help to promote safety or decrease risk, and foster continued public trust in the FDA's assessments. In advancing regulatory science, the FDA recognizes the importance of collaborations between government researchers and regulators, industry, stakeholders, and academia to ensure that the most promising technologies are identified, developed, validated, and integrated into regulatory risk assessment.

Advances in bioengineering and material sciences, microfabrication, and microfluidics technologies have enabled the development of microphysiological systems that mimic functional units of an organ. These advances have made it possible to initiate the engineering of cellular environments and/or functional units of lung, heart, blood vessels, muscles, bones, liver, nervous system (including eye), gut, and kidney. In general, these microsystems reflect human physiologically relevant parameters, including proper cell-to-cell, cell-to-matrix, biochemical, and mechanical signaling, but lack the complex architecture of tissues and organ system interactions.[2–7]

The National Center for Advancing Translational Science (NCATS), the FDA, and the Defense Advanced Research Projects Agency (DARPA) partnership for the development of in vitro microphysiological systems was a groundbreaking example of the types of partnerships that are needed to bring innovative new technologies into the regulatory paradigm. NCATS, the FDA, and DARPA collaborated to develop organs on a chip to screen for safe and effective products that was far more swift and efficient than current methods. NCATS identified barriers to progress and provided science-based solutions to reduce costs and the time required to develop new drugs and diagnostics. The FDA helped determine how this new technology can be used to assess drug safety, before approval for first-in-human studies. DARPA and NCATS facilitated collaborations between researchers and the FDA to advance the goals of both programs. NCATS and DARPA, in coordination with the FDA, solicited proposals from industry, government laboratories, academic institutions, and other research organizations on how best to develop the chip technology by bringing together the latest advances in engineering, biology, and toxicology to bear on this complex problem. Throughout the 5-year research plan, NCATS, the FDA, and DARPA met biannually with all the researchers.

This was a unique partnership because it involved regulatory scientists at the very beginning and during all stages of test method development. Regulatory scientists were able to address identified gaps in the knowledge needed to regulate FDA products and how organs on a chip, if validated, could provide important information to fill those gaps.

Microphysiological systems (organs on a chip) that reconstitute tissue–tissue interfaces critical to organ function can expand the capabilities of cell culture models and provide relatively low-cost and more informative alternatives to animal toxicology studies. For example, the gut on a chip, which was designed to mimic the dynamic mechanical microenvironment of the gut and enable analysis of intestinal epithelial barrier functions in vitro. The ability of the human gut on a chip to mimic the 3-dimensional structure, differentiated cell types, and multiple physiological functions of the normal intestinal wall may provide a powerful new tool for regulators to answer questions that currently cannot be resolved using either animal models or human studies (eg, compound bioavailability, microbiome–drug interactions). In vitro microphysiological systems, in general, if accepted as a new tool for use in a regulatory setting, may have the potential to be an exciting new tool to address these concerns and could assist in bringing safe products to the market.[8–10]

We should consider that not all new technologies are appropriate for use in a regulatory research environment and some may have to be modified to conform to the strict regulatory demands for generating information that may be used to address public health concerns. One often hears the terms *validation* and *qualification* accompanying new methods or systems being used in a regulatory testing environment. Validation means that the product will produce results that are consistent and also that the product consistently will meet predetermined specifications or attributes. Validation is an evaluation process that assesses the assumptions, relevance, reliability, reproducibility, and sensitivity of a test, or series of tests, for regulatory use. Current formal approaches to validation involve lengthy and expensive processes that require validating in vitro data against in vivo data. Qualification is a subset of validation and is a process that ensures that something complies with a predetermined outcome or set of requirements. Regulators must determine if a new tool is qualified to make safety decisions that potentially could affect millions of consumers. Once a new tool is qualified for a specific context of use, industry and other stakeholders can use the tool for the qualified purpose during product development, and FDA reviewers can be confident in applying the tool without needing to review the underlying supporting data each time a tool is used.

The bottom line is that confidence is needed in the performance of any new tools that are used to demonstrate safety. However, for the microphysiological test systems, the traditional validation approach may not be relevant for the in vitro microphysiological systems. Rather, a "context of use"[11] approach may be sufficient and appropriate for qualification. Context of use refers to a clearly articulated description delineating the manner and purpose of use for the tool or when and how will it be used. This approach also defines the boundaries of the available data that adequately justify the use of the tool. Models and assays, in general, inevitably are associated with limitations. Knowing these limitations allow one to define the context in which results are intended to be used and the specific human outcomes that will be predicted. In general, there is a considerable amount of work that must be performed before any new technology will be accepted as a now regulatory research tool.

On April 11, 2017, the FDA announced a multiyear research and development agreement with a company called Emulate Inc, (Boston, MA) to evaluate the company's organs-on-chips technology in laboratories at the agency's Center for Food Safety and Applied Nutrition (CFSAN).

CFSAN researchers are evaluating the effectiveness of this technology to better understand the usefulness of this technology in predicting the effects of chemicals and other potentially harmful materials on the human body. CFSAN researchers will look at the concordance of the data from this research platform with data on the same compounds from in silico, in vivo, and other in vitro test systems. CFSAN will begin to develop general principles for use to consider as these new tools are incorporated into regulatory use.

CFSAN and the FDA are excited to be at the forefront of this groundbreaking research, which one day may be used routinely to safeguard public health.

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Conflicts of interest
The authors disclose no conflicts.


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