Development and Use of Advanced Testing Approaches by the U.S. FDA

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Challenges to FDA

* Recent breakthroughs in science and technology have the potential to transform our ability to prevent, diagnose and treat disease.
* However, major investments in basic and translational research are not efficiently yielding new products needed to benefit patients/populations.
* Product development is increasingly costly, success rates remain low, many uncertainties exist, including, as a major component, failures in predicting toxicity despite extensive animal testing.
What is Regulatory Science?

* The application of science to the development and utilization of new tools, standards, and approaches for the assessment of product efficacy, safety, and quality

* Critical to effectively translate cutting-edge developments in science and technology into promising products and therapies.

The Tipping Point for Toxicology

* Change often involves a pivotal event that builds on previous history and opens the door to a new era.

* Publication of the NAS report was the “tipping point” for a change in toxicology.

* Validation of these new methods for regulatory use— -the critical component in ensuring the vision’s success.

What does this Mean for the Regulatory Toxicologist?

- Unique opportunity for developing more predicative models of human toxicity
- But need to have confidence in the data from these new approaches

Limitations of Current Validation Strategies

- Clear that in vivo animal studies may not be the gold standard that new toxicology methods are compared against.
- Need to determine the relevance of in vitro results to what occurs in humans rather than what occurs in rodents and other test animals.
Limitations of Current Validation Strategies

- Clear that the purpose of each test in the regulatory paradigm must be taken into consideration.
- Consequently applying a “one size fits all” approach to validation is not conducive to the rapid incorporation of emerging science into the regulatory decision-making framework.

Partnerships - NIH/FDA Regulatory Science Initiative

- FDA and NIH launched a new regulatory science grant program, including support for novel approaches for transforming toxicology.
- An important feature of this program is ongoing FDA and NIH staff engagement with the grantees/innovator.
- Research funded through the NIH/FDA Common Fund.
Partnerships-NIH/FDA Common Fund Grants-New Testing Approaches

* Integrating “organ on a chip” microdevices to produce a Heart-Lung Micromachine” for real-time measures of the efficacy, bioavailability & safety of aerosol-based drugs, nanotherapeutics and other medical products

Wyss Institute Lung Microdevice Unique Features

* Places two layers of living tissues – the lining of the lung’s air sacs and the blood vessels that surround them – across a porous, flexible boundary.

* Air is delivered to the lung lining cells, a rich culture medium flows in the capillary channel to mimic blood, and cyclic mechanical stretching mimics breathing.
Wyss Heart-on-a-chip
Unique Features

* Design of a “heart-on-a-chip” exploits muscular thin film technology
* Biohybrid constructs of an engineered, anisotropic ventricular myocardium on an elastomeric thin film – to measure contractility, combined with a quantification of action potential propagation, and cytoskeletal architecture in multiple tissues in the same experiment
* Real-time data collection and analysis during pharmacological intervention.

Partnerships-Critical Path Grants

* The Critical Path Initiative is FDA’s national strategy for transforming the way FDA-regulated medical products are developed, evaluated, and manufactured.
* Recently awarded four critical path grants- two for biomarker qualification and two for new models to assess reproductive and/or developmental toxicology
Alternative Models for Reproductive and Developmental Toxicity

* Establish in vitro alternative model for evaluating male reproductive toxicity by using a 3-dimensional culture that resembles organs in structure

* Develop a testing strategy of combined assays to screen chemicals using aggregate brain cell cultures

Partnerships-FDA NIH DARPA

* To jointly develop new tools that can be used in therapeutic development

* Create a collaboration of government, academic and industry scientists working together on new toxicology tools
Integrated Microphysiological Systems for Drug Efficacy and Toxicity Testing in Human Health and Disease

* The focus is the development of physiologically and pathologically accurate human models of any organ system using tissue engineering platforms that either already exist or are being developed simultaneously through the DARPA initiative.

Microphysiological Systems
DARPA –BAA-11-73

* Reconfigurable platform
* Ten or more in vitro physiological systems
* Able to monitor resident tissues for up to 4 weeks
* Uses human cells
* Commercial availability
* Includes plan for validating integrated platform performance
* 70 million over 5 years
Stem/Progenitor Cell-Derived Human Micro-organs and tissues

The focus is the development of *in vitro* multi-cellular models of human physiology that provide advancements over current human stem- and progenitor-derived cell-type selectivity approaches through improvements in differentiation efficiencies, cell-type diversity, genetic complexity and utilization of 3D culturing approaches to enhance cellular microenvironments. http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-12-001.html

NIH-DARPA-FDA Partnership

* Parallel programs with DARPA
* Developing new tools that can be used in therapeutic development
* Facilitate collaboration between researchers and FDA to advance the goals of both programs
* FDA will help determine how this new technology can be used to assess product safety
FDA/DARPA/NIH International Workshop on Organs/Human on a Chip

- Workshop will take place at FDA on January 24-25, 2013.
- Workshop will be web-cast and also recorded.
- Planning committee being formed
- More details to come

Qualification-Moving new science into regulation

- Current formal approaches to validation involve lengthy and expensive processes that require validating in vitro data against in vivo data.
- Not relevant for all new pathways and endpoints being measured.
- New science-based approaches to qualification required—“Fit for purpose” qualification
An example of a new validation strategy is the FDA Drug Development Tool (DDT) Qualification Process.

The FDA DDT Qualification Program involves a “fit-for-purpose” qualification process.

Once a DDT is qualified for a specific context of use, industry can use the tool for the qualified purpose during product development, and FDA reviewers can be confident in applying the DDT to make regulatory decisions.
Moving Forward Together

* Investments in regulatory science can enable FDA to better protect and promote the public health.

* FDA does not want to be “on the sidelines” watching but an active participant in development of new methods and approaches

* Moving to newer methods is challenging: Collaboration is essential to define needed pathways and catalyze change