How does implementation of FDA’s Predictive Toxicology Roadmap impact risk assessments of drugs?

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This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
FDA’s Predictive Toxicology Roadmap
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- FDA’s Predictive Toxicology Roadmap
- https://www.fda.gov/science-research/about-science-research-fda/fdas-predictive-toxicology-roadmap
Why a Roadmap?

• Advances in systems biology, stem cells, engineered tissues, and mathematical modeling are creating unique opportunities to improve toxicology’s predictive ability, potentially enhancing FDA’s 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.
Why a Roadmap?

- Each of FDA’s product centers has very different legal authorities for evaluation of product safety.
- Nevertheless, greater cross-center collaboration can potentially help with the assessment of emerging predictive toxicology methods which may lead to use of such technologies in particular regulatory contexts.
- So a roadmap can describe those common areas of interest and help coordinate advancement of new approach methodologies.
What is the roadmap? What isn’t the roadmap?

• Is a high level document – think highways not neighborhood streets
  – Not a check list of things to do to get an assay accepted
  – Because of the differences between the centers and the regulated products, there is not a single pathway for adoption of new approach methodologies.
A Six-Part Framework for New or Enhanced FDA Engagement in the Science of Toxicology

1. Organizing Committee – Toxicology Working Group
2. Training
3. Continued Communication
4. Collaborations
5. Research
6. Oversight
FDA Predictive Toxicology Roadmap

Key points

• Toxicology Issues that Need Addressing for FDA-Regulated Products
• Toxicology Areas That Could Benefit from Improved Predictivity
• Context of Use
• Qualification
• Promising New Technologies in Predictive Toxicology
Why identify “Toxicology Issues that Need Addressing for FDA-Regulated Products”?

• Because an assay that can’t provide answers to relevant questions will not be of use.
• No point in qualifying or validating an assay that will not have regulatory use.
• Starting with data needs can avoid wasted efforts.
Toxicology Issues that Need Addressing for FDA-Regulated Products

• Don’t start with the technology
• Start with the needs
  – Identifying dose levels or systemic exposures at which no adverse effects are observed
  – Determining a reasonably safe first-in-human dose for human pharmaceuticals
  – Identifying potential target organs of toxicity
  – Identifying potential developmental and reproductive toxicity
  – Identifying potential carcinogenicity
  – Identifying and understanding the factors that affect different responses by sub-populations
Use of nonclinical data in drug development

Lead Compound Selected

Starting Clinical Dose Selected

Discovery

IND supporting studies

Additional nonclinical studies

Clinical trials

Phase 1
- Safety PK
- Dose ranging

Phase 2
- Safety PK
- Efficacy

Phase 3

Marketing Application

FDA Review

Screening pharmacology
Proof of concept
Screening toxicity
In vitro and in vivo

Safety pharmacology
Single or repeated dose toxicity
Genotoxicity

Genotoxicity
Repeated dose toxicity
Developmental and reproductive toxicity
Carcinogenicity
Drug development nonclinical needs – more detail on IND supporting studies

- Safety pharmacology (ICH S7A and B)
  - CNS effects - seizures
  - Cardiovascular effects - arrhythmias
  - Respiratory effects
- Single or repeated dose toxicity (ICH M3 and S6)
  - Start dose selection
  - Target organ identification
  - Biomarker identification
  - Histopathology
- Genotoxicity (ICH S2)
  - Direct DNA damage
  - Clastogenicity – mammalian cells and in vivo
- Developmental and reproductive toxicity (ICH S5)
  - Fertility
  - Embryofetal effects
  - Pre/postnatal effects
- Carcinogenicity
  - 2 species
Drug development nonclinical needs

• For most nonclinical endpoints an understanding of in vivo exposure at which a finding occurs is needed to compare to human exposures.

• Characterization of effects in an integrated system to identify interactions
  – Metabolism
  – Immune interactions and immune mediated toxicity
  – Organ innervation
  – Hormonal effects

*These needs are difficult to meet with in vitro systems.*
Roadmap recognizes “Toxicology Areas That Could Benefit from Improved Predictivity”

- 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
- Et cetera

List is not comprehensive or prioritized.
Context of Use and Qualification

• 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).

• 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 and Qualification

- **Context of use**
  - An assay or model does not have to do everything
  - What question needs to be answered and for what purpose?
  - Define applicability domain and limitations
  - Context could be expanded over time

- **How much “validation” is needed for a particular assay will depend on the particular context of use.**

Replacement of pivotal nonclinical safety study

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Discovery/Screening
Utility, qualification and complexity of an assay is driven by its context of use

• What question needs to be answered and for what purpose?
  – Screening to select a lead compound versus supporting studies in human (What is the starting dose?)
  – Does this molecule have the desired pharmacologic action?
  – Does this molecule lack any toxicity potential versus does it lack a specific toxicity?
  – Can I give this drug safely to a woman that might become pregnant?
Stone Age  Bronze Age  Iron Age  Space Age

They are all hammers. But which tool is right for the job?
Questions to be answered can drive how complex a model needs to be.

- **2D cultures**
  - cells
  - culture media
  - 2D dishes (Petri dish)
  - extracellular adhesive proteins

- **3D organoids**
  - multiple cell types
  - cell-cell interactions
  - extracellular proteins
  - extracellular remodeling

- **microphysiological systems**
  - organoid technology
  - microfabrication of dedicated chambers
  - microfluidic circulation of media

- **Organs and tissues in vivo**
Roadmap recognizes “Promising New Technologies in Predictive Toxicology”

- Microphysiological systems like tissues or organs on a chip
- Alternative test methods for reproductive toxicity testing
- Computational toxicology
- In vitro alternatives
- Quantitative risk assessment (QRA) addressing the complex chemical mixtures of tobacco products
- Read across methodology
CDER is optimistic but realistic about new approach methodologies.

Gartner Hype Cycle, Gartner, Inc., 2017

- Innovation Trigger
- Peak of Inflated Expectations
- Trough of Disillusionment
- Slope of Enlightenment
- Plateau of Productivity

Plateau will be reached in:
- less than 2 years
- 2 to 5 years
- 5 to 10 years
- more than 10 years
- obsolete before plateau
How I would create my own “Hype cycle for transgenic carcinogenicity studies”

In my view:

- Some transgenic mice or other models found or developed to be susceptible to tumor formation is at the beginning of the Innovation Trigger.
- HESI validates several models is in the middle of the Innovation Trigger.
- ICH includes “short- or medium-term in vivo rodent test systems” for carcinogenicity and Companies begin using models are on the Peak of Inflated Expectations.
- Neonatal model seldom, XPA-/- Mice seldom used, Stability issues with Tg.AC transgene, Interpretation issues with Tg.AC, and P53+-/- mice limited to genotoxic drugs are all leaving the Peak of Inflated Expectations and traveling into the Trough of Disillusionment.
- Most mouse studies are in hemizygous Tg RasH2 has reached the Plateau of Productivity.
MPS, Tissue Chips, Organ-on-a-Chip

There are a lot of companies entering this area!

Random sample – none endorsed by FDA
FDA’s Predictive Toxicology Roadmap
2018 Annual Report
Prepared by the Food and Drug Administration’s Toxicology Working Group

Table of Contents
- Executive Summary
- Research
- Workshops
- Guidance
- Cross-Agency Activities
- Presentations Publications
- Conclusion
Comprehensive in vitro Proarrhythmia Assay (CiPA)

• Current paradigm for assessing proarrhythmic risk is largely based on assessing one cardiac ion channel and whether a drug prolongs the QT interval on the ECG (ICH S7B and ICH E14)

• Some limitations to this approach – may be too conservative

• CiPA initiative is an FDA, Cardiac Safety Research Consortium and HESI collaboration with participation from EMA, Health Canada, PMDA and industry from all the regions
Components of CiPA

- **In vitro Assessment of Drug Effects in Multiple Ionic Currents**
  - Sodium
  - Calcium
  - hERG
  - Potassium

  - $I_{Ks}$ and $I_{Na}$ Peak in specific situations

- **In silico Computer Modeling to Predict Risk**
  - $I_{slim} = C \frac{dV_m}{dt} + I_m$

  - Torsade Metric Score (qNET)

- **In vivo ECG Biomarker in Phase 1 Clinical Trials**
  - ECG
  - baseline
  - on drug

  - Check for unanticipated human effects, confirm mixed channel effects using $JT_{peakc}$

- **In vitro effects on Human Stem Cell Derived Ventricular Cardiomyocytes**

  - Can be considered for unanticipated nonclinical effects, or if human ECG data is insufficient

Modified from Jose Vicente
CiPA may become part of ICH guidance

• A question and answer document is being developed for ICH S7A and E14, the guidances dealing with cardiovascular safety pharmacology and clinical evaluation of proarrhythmia.
• This Q&A may introduce CiPA to the testing approach.
History of FDA’s Involvement with MPS

• In 2011 DARPA funded MPS research. “DARPA involved the FDA from the beginning of the MPS program to help ensure that regulatory challenges of reviewing drug safety and efficacy are considered during development of the MPS platform”

• In 2012 NCATS funded the Tissue Chip Development Program. FDA has been a partner throughout the program
  – https://ncats.nih.gov/tissuechip/about

• Critical to have regulators at the table from the beginning if aim is to use method for regulatory use
FDA scientists are developing in-house MPS and collaborating with several external partners
In Vitro Systems Working Group (IVSWG)

- Office of Chief Scientist, Office of Commissioner

- Discuss *in vitro* activities across FDA

- Interact with U.S. federal partners and global regulatory partners to facilitate discussion, development, and acceptance of regulatory performance criteria for such assays
In Vitro Systems Working Group (IVSWG)

- Establish a dialogue and develop partnerships with FDA stakeholders to explore regulatory science applications for such technologies

- Leadership Council
  - Researcher Work Group (User Group)
  - Performance Criteria Development Work Group (Regulatory Group)
Performance Criteria Development Working Group

• Representatives from each FDA Center/Office

• Collaborate with the Researcher Working Group to translate proposals into draft performance criteria

• Discuss draft performance criteria within FDA and with FDA stakeholders to obtain broad feedback and refine the draft criteria
IVSWG First “Case Study”

• Focus on coordinating, developing, and evaluating *in vitro* Microphysiological Systems (MPS) for regulatory use

• This will be the first IVSWG case study on the viability of its implementation plan for FDA’s Predictive Toxicology Roadmap

• IVSWG program will be evaluated, and if needed, refined, after completion of its goals
Objectives of the IVSWP MPS Program

- Define agreed-upon terminology for MPS and research/regulatory gaps for which MPS may be useful
- Identify partnerships to advance MPS technology
- Develop draft performance criteria for MPS and then with stakeholders
- Develop a Request for Information for MPS Developers and End Users
Webinar Series on Emerging Predictive Methods

• Opportunity for developers/users to present new methods and methodologies to FDA

• Webinars will be advertised ONLY to FDA scientists

• If selected as a webinar:
  – participation in FDA’s webinar series would not constitute the agency’s endorsement of a new method or methodology
  – it would not mean that FDA would assist the developer in qualifying his/her new method for regulatory use

• Check our website for announcement
  – https://www.fda.gov/science-research/about-science-research-fda/fdas-predictive-toxicology-roadmap
Drug development tool qualification at CDER

- **Types of Tools:**

  - **Clinical Outcome Assessments**: Potential for wide applicability to support drug development programs.
  - **Biomarkers**: Usually in narrow context of use (biological, radiological threats).
  - **Animal Models (Animal Rule)**
21st Century Cures legislation: Section 507
Qualification of Drug Development Tools

• 21st Century Cures and PDUFA VI increasingly places FDA as an active participant in drug development, broadening our traditional regulatory role

• Formalizes a three-step submission process. FDA can Accept/Not Accept at each stage:
  – Letter of Intent
  – Qualification Plan
  – Full Qualification Package

• A transparent process – so all stakeholders are aware of tools in development, stage, and FDA determinations/recommendations

• Requires setting and implementing “reasonable timeframes” for submission review/decision
How does implementation of FDA’s Predictive Toxicology Roadmap impact risk assessments of drugs?

• The roadmap is less than 2-years old so direct evidence of new impact is limited – it takes time to develop new methods – although many existing programs fit the concepts outlined.

• The roadmap provides a framework for thinking about new approaches and emphasizes the Agency’s commitment to incorporating the best predictive toxicology methods into regulatory use.
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