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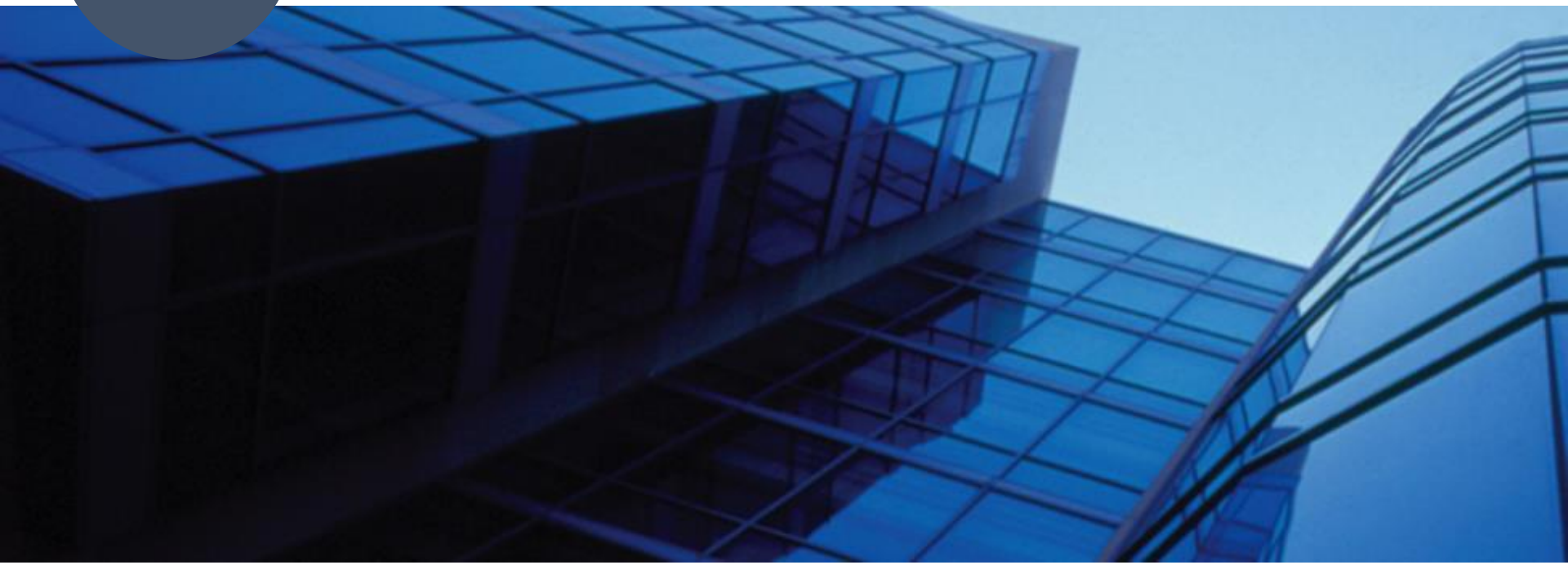

We need an evolution to spark a revolution: what animal lawyers can and should do to sunset the use of animals in scientific research, toxicity testing and drug development

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Presentation Overview

- What is our ultimate goal and how do we get there?
- What is “research?”
- Four fields of laws that require scientific data
  - Cosmetics
  - Environmental Chemicals
  - Drug Development
  - Discovery research
- Short-comings of current federal and state laws on alternatives to animals in science
- The path forward and the role of the legal community

The ultimate goal – absolute replacement

Replace science that uses non-human animals with non-living systems that more accurately recapitulate(recreate) human responses to improve data and decision making.

How do we get there?

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What is research?

Four fields of law that require scientific data

Laws that create a demand for non-human animal science

- Cosmetics
  - Skin and eye irritation and sensitization
  - Skin penetration
  - FFDCA – no pre-market approval

- Chemicals in commerce and pesticides
  - Numerous endpoints, driven by human carinogenicity
  - Laws:
    - ✓ TSCA
    - ✓ FIFRA
    - ✓ Some state laws (California Proposition 65)

- Drugs and devices
  - "Safe and Effective" products
  - Numerous endpoints for toxicity, including liver and heart damage
  - FFDCA – premarket approval needed

- Discovery research – new knowledge
  - Largely NIH funded (budget = about $42 B/year)
  - Data not produced for statutory decision making

Why does this matter?

Current federal and state alternatives laws

Conditional mandates

- TSCA alternatives provision, section 4(h)
  - EPA shall reduce and replace, to the extent practicable, scientifically justified, and consistent with the policies of this subchapter, the use of vertebrate animals in the testing of chemical substances or mixtures under this subchapter …

- State laws that require the use of scientifically valid alternatives (e.g., Virginia)
  - § 3.2-6592 (A). No manufacturer or contract testing facility shall use an animal test method when an alternative test method is available.

  - § 3.2-6591. Definitions. "Alternative test method" means a test method that (i) provides information of equivalent or better scientific quality and relevance than animal test methods, (ii) has been identified by a validation body and adopted by the relevant federal agency or program within an agency responsible for regulating the specific product or activity for which the test is being conducted, and (iii) does not use animals, or, when there is no test method available that does not use animals, uses the fewest animals possible and reduces the level of suffering or stress, to the greatest extent possible, of an animal used for testing. "Alternative test method" includes computational toxicology and bioinformatics, high-throughput screening methods, testing of categories of chemical substances, tiered testing methods, invitro studies, and systems biology and new or revised methods.

What should lawyers do?

Three key actions

- Advocate to enact laws that **incentivize** the development, use, validation and regulatory acceptance of absolute replacements.
  - Eg., Humane Research and Testing Act (H.R. 1744)
  - Appropriations/funding specifically for non-animal alternatives
- **Eliminate barriers** in current laws that require animal use
  - E.g., FDA Modernization Act (S. 2952. HR. 2565)
- Address issues associated with **potential liability** due to using data from non-animal methods in decision making

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ACKNOWLEDGEMENTS

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Author notes

Comments (0)

JOURNAL ARTICLE CORRECTED PROOF

Use of Human iPSC-CMs in Nonclinical Regulatory Studies for Cardiac Safety Assessment

Xi Yang ✉, Alexandre J S Ribeiro, Li Pang, David G Strauss Author Notes

Toxicological Sciences, kfac095, https://doi.org/10.1093/toxsci/kfac095

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Abstract

Human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) provide a human-relevant platform for cardiac function assessment. Alternative assays using hiPSC-CMs are increasingly being employed for regulatory decision-making. A retrospective review revealed steady use of hiPSC-CM-based *in vitro* assays in nonclinical studies of drug-induced cardiotoxicity in regulatory submissions to the U.S. Food and Drug Administration (FDA). Most of the hiPSC-CMs data were obtained in exploratory studies and submitted as supportive evidence in concordance with other nonclinical data. Some of those studies were used to inform clinical trial design. This article provides an overview of the use of hiPSC-CMs in regulatory applications to FDA, with a focus on the integration of human-relevant *in vitro* data into proarrhythmic and non-proarrhythmic risk assessment. By identifying the regulatory submissions including hiPSC-CMs data, we explore their utility and discuss their limitations for predicting human cardiac safety in clinical trials. An important take-home message is that regulatory acceptance of hiPSC-CMs data is dependent on both the context of use and accurate data interpretation.

Keywords: cardiovascular toxicity, *in vitro* models, regulatory sciences, translational sciences

Issue Section: Contemporary Review

The ultimate goal – absolute replacement

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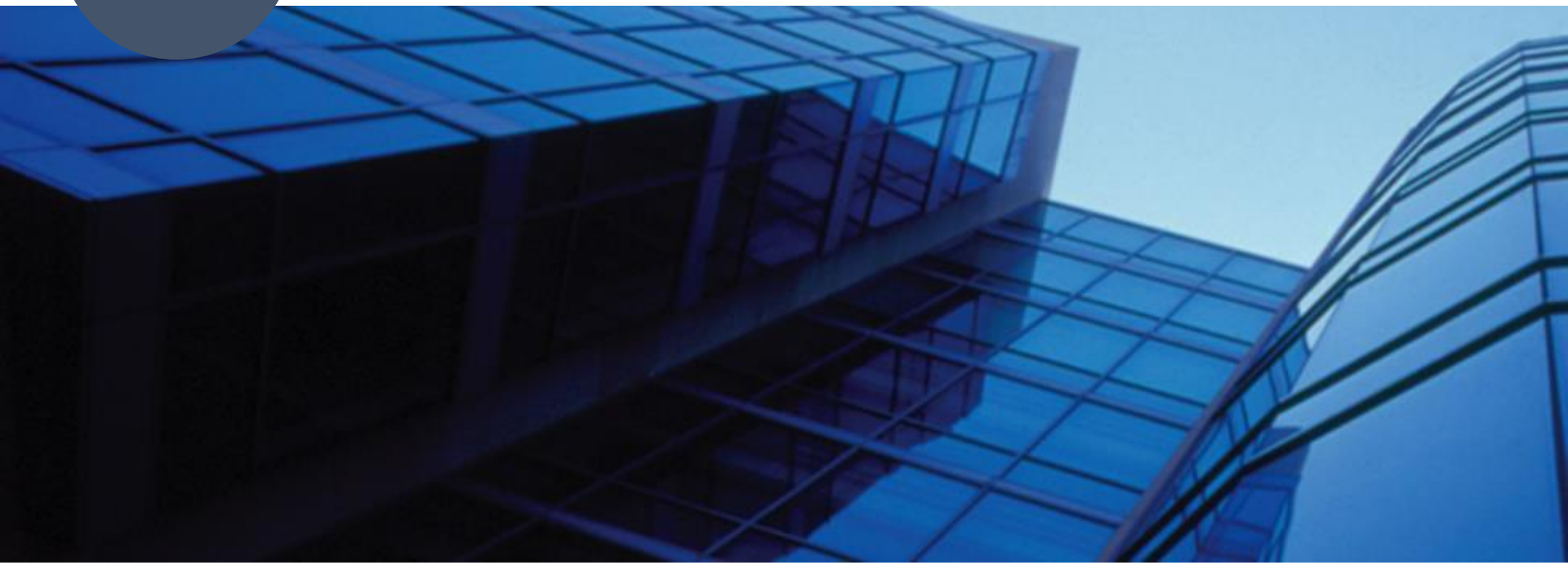

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