



May 17, 2017

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Dear Dr. Casey:

The following comments are submitted on behalf of Center for Responsible Science (CRS), and Safer Medicines Trust (SMT). We appreciate the opportunity to submit these written comments. We applaud ICCVAM's progress, and Dr. Casey's continued open-door policy and willingness to interact with stakeholders.

CRS and SMT promote advances in regulatory science including the use of modern, effective preclinical test methods to streamline development and bring safer, more effective products to market more quickly at less cost.

Participation and Cooperation of Agency Representatives and Stakeholders is Essential to the Success of Roadmap Effort

We are pleased with ICCVAM efforts and vision "to establish new approaches for evaluating the safety of chemicals and medical products in the United States that will increase confidence in alternative methods and improve their relevance to human health outcomes while maximizing efficiency and maintaining a commitment to replace, reduce, and refine animal use."¹ A coordinated effort involving all agencies, academia, industry and non-governmental organizations is required to implement this vision for toxicity testing in the 21st Century.

We are concerned that there is an unequal effort among ICCVAM member agencies to participate in the Strategic Roadmap effort. Without full participation of agencies in these efforts, progress will be stymied. It is our sincere hope that FDA regulators and

¹ Strategic Roadmap: New Approaches to Evaluate the Safety of Chemicals and Medical Products, U.S. Department of Health and Human Services, National Toxicology Program. <https://ntp.niehs.nih.gov/pubhealth/evalatm/natl-strategy/index.html>

drug and device sponsors become fully engaged and work together to implement the “vision” and that FDA communicate its efforts and accomplishments.

We are pleased to learn of FDA’s Cooperative Research Agreement (CRADA) with Emulate, Inc. to evaluate and qualify organs-on-chips technology for toxicology testing for FDA regulated food, dietary supplements and cosmetics. We hope this collaboration will expand to pharmaceuticals.

Additionally, it is imperative that sponsors make their drugs available to be tested in human-relevant platforms, especially drugs that have caused serious adverse events and death in clinical trials and post-marketing.

Advancing Innovation and use of Human-Relevant Test Methods for Drugs and Devices through Reasonable Regulation Updates

Current FDA regulations and perceived regulatory expectations create a barrier to integrating human-relevant approaches to preclinical testing for medical products. There is a widespread perception among sponsors that regulatory authorities require animal data, when, in fact, what they actually require is a degree of assurance that a particular substance will not cause harm. There is a pressing need for a clearer understanding of actual regulatory requirements.

As stated in our comments last year, CRS, SMT and twelve additional patient advocacy groups, technology developers and non-profit organizations² petitioned FDA³ in 2015 to update twenty-nine regulations to allow the use of the preclinical test method most predictive of human response. Petitioners’ modest, non-controversial proposed regulatory amendments would be an important first step to overcome a substantial roadblock to adoption and use of human-relevant test methods. Petitioners merely seek an acknowledgement of regulatory acceptance of modern test methods in appropriate circumstances by modifying current regulatory language to change it from animal focused to “test-neutral” language. CRS has made numerous requests to meet with FDA to discuss the petition and all requests, thus far, have been ignored.

The FDA regulations as currently written promote the status quo, creating an unreceptive environment that fails to encourage innovation and development of more predictive test methods. Modification of regulatory language is needed to clear up confusion, broaden testing options for sponsors, and spark innovation of more predictive methods.

² Asterand Bioscience, AxoSim Technologies LLC, Empiriko, Friends of Cancer Research, HµREL® Corporation, In Vitro ADMET Laboratories, Invitro Cue, InVitro International, MatTek Corporation, NORD (National Organization for Rare Disorders), United Spinal Association, and 3D Biomatrix, Inc.

³ Requests that the FDA modify existing regulations in CFR Title 21 that governs requirements for investigational new drug applications, investigational device exemptions, and new drug applications. <https://www.regulations.gov/#!docketDetail;D=FDA-2015-P-2820>

Recent events underscore the need for more predictive preclinical tests and regulations that allow their use. Human participants in clinical trials are exposed to risks of adverse events, including death and disability. Accordingly, the regulations must be updated to ensure that drug and device sponsors have the confidence to use the most predictive preclinical test available, whether animal or non-animal.

CRS has amended the petition each year since it was filed to include information about clinical trial deaths due to unexpected toxicities that were not predicted with traditional preclinical testing. Additionally, the father of the first clinical trial participant to die of cerebral edema in the Juno Therapeutics CAR-T ROCKET Trial in May 2016, joined the petition in the latest amendment filed with FDA.

Treatment-related Clinical Trial Deaths

- **Juno Therapeutics (5 deaths)** – On May 24, 2016, 24-year-old clinical trial participant Max Vokhgelt died from cerebral edema, likely brought on by a cytokine storm in a phase II trial for a chimeric antigen receptor T-Cell (CAR-T) therapy. Max's death was not reported until July 13, 2016, after two more participants died from cerebral edema. FDA issued a clinical hold of the trial on July 7, 2016, but lifted the hold just five days later based on Juno's assertion that the chemotherapy preconditioning agent (fludarabine) in combination with the CAR-T therapy had caused the deaths. Juno resumed the trial without fludarabine, and two more clinical trial participants died from cerebral edema in November 2016.
- **Ziopharm (3 deaths)** – On July 14, 2016, three deaths were reported that occurred in a phase I trial for a gene therapy for brain tumors.
- **Seattle Genetics (4 deaths)** – In late December 2016, four more deaths from hepatotoxicity in a cancer drug trial prompted FDA to issue a clinical hold.
- **Stemline Therapeutics (4 deaths)** – In February 2017, Stemline Therapeutics announced the death of one patient in a phase II trial for blastic plasmacytoid dendritic cell neoplasm (BPDCN). This was the third death from capillary leak syndrome in this trial. In March, a fourth death was announced.
- **Kite Pharma (4 deaths)** – In December 2016, Kite Pharma announced there had been three treatment-related deaths in their ZUMA-1 CAR-T trial. On May 8, 2017, Kite reported another death in its ZUMA trial, this time from cerebral edema.

Despite the promise as a breakthrough cancer cure, there are serious safety concerns related to CAR-T cell therapies.⁴ Lack of relevant animal models for safety testing has been exemplified by numerous serious adverse events in studies using CAR-T

⁴ FDA Proposes New Databases to Monitor CAR T-Cell Safety Across INDs. RAPS, March 16, 2016. <http://www.raps.org/Regulatory-Focus/News/2016/03/16/24549/FDA-Proposes-New-Databases-to-Monitor-CAR-T-Cell-Safety-Across-INDs/>

engineered cells.⁵ It is essential that this promising cancer therapy be tested in human-relevant test methods to more specifically determine the safety risks before it is tested in humans.

There are human-relevant test methods that can predict cytokine release syndrome and inflammation-related adverse events, including cerebral edema.⁶ CAR-T therapies could be tested in this platform in combination with any preconditioning drugs. However, due to current FDA regulations, the animal tests are required. It's clear that traditional animal tests could not predict the deadly cerebral edema that killed six in the Juno ROCKET and KITE ZUMA-1 trials.

Growing Disparity Between Scientific Advancement and Regulatory Policy Needs to be addressed

The 2016 SACATM meeting focused on developing a strategy for implementing the vision for toxicity testing in the 21st Century. One of the main topics discussed by committee members and meeting participants was the need for regulation change.

As noted in the document developed for the SACATM meeting:

“Over the ensuing decade, significant investments in technology development and biomedical research have resulted in many transformative scientific breakthroughs necessary for implementing the NRC vision. However, these advances have yet to be met with a concomitant increase in our ability to more accurately predict the adverse human health effects caused by ubiquitous exposure to xenobiotic chemicals, whether alone or in mixtures. This limited translational impact is attributable, at least in part, to rapid scientific advancements outpacing the change in institutional standards required for their effective utilization. Specifically, legacy test methods and classification systems developed using animal models cannot always evaluate the nuances of human pathophysiology and genetic variability important for modern safety and risk assessment. Ironically, however, the institutionalized use of animal-based methods is now preventing more human-predictive approaches from being developed and adopted by Federal agencies

⁵ *Preclinical Models Evaluating the Safety and Efficacy of Candidate T Cell Immunotherapies for Human Clinical Trials*, American Society of Gene and Cell Therapy, Translational Science and Product Development, Volume 1, Issue 12, July 2014

<http://www.asgct.org/the-vector/volume-1-issue-12-july-2014/meeting-center/translational-science-and-product-development>

⁶ <http://www.asgct.org/the-vector/volume-1-issue-12-july-2014/meeting-center/translational-science-and-product-development>

⁶ BioMAP® - Complete Phenotypic Drug Discovery Solutions
<https://www.discoverx.com/services/drug-discovery-development-services/primary-cell-phenotypic-profiling/biomap-phenotypic-drug-discovery-solutions>

and industry. **Left unaddressed, this growing disparity between new scientific advancement and regulatory policy could soon impede our ability to capitalize on the remarkable knowledge and tools arising from projects such as ToxCast, Tox21, Human Tissue Chips, and the Precision Medicine Initiative.**⁷

Major limiting factors for implementing 21st century approaches to toxicity testing include policy and regulation. CRS' proposal to make modest, non-controversial regulation amendments would be an important first step to overcome this limiting factor without protracted planning, discussion and resources. Clearly there is a need to overcome all of the additional roadblocks to adoption of human-relevant test methods, and a concerted, coordinated effort is needed. However, in the context of FDA regulated drug and device development, minor amendments to outdated existing regulations would have great impact on the use and development of better tools for drug and device development, which could save lives.

A common theme expressed at the SACATM meeting was the need for regulatory acceptance to enable implementation of the Vision for Toxicity Testing in the 21st Century. Below are just a few examples of what was expressed by SACATM members and presenters:

- Dr. Warren Casey, NIEHS: “It is difficult for evolving institutional practices to keep pace with revolutionary advances in science and technology.”⁸
- Tim Malloy, UCLA: “The leading perceived barrier was regulatory acceptance.” (Used FDA as an example).⁹
- Katherine Willett, SACATM member: “Language at the regulatory level, we’ve discussed that a lot today, these are changing slowly with time, as the regulations are being updated, updating regulations is a years-long process, nevertheless, I think now is the time that a lot of the regulations that stipulate animal testing could be revised to make that language more neutral, as

⁷ SACATM Background Document: A Strategy for Implementing the Vision for Toxicity Testing in the 21st Century.

http://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2016/september/vision20160927_508.pdf

⁸ National Toxicology Program website, SACATM Meeting videos. **Strategy for Implementing the Vision for Toxicity Testing in the 21st Century:** Dr. Warren Casey at 9:51

<https://ntp.niehs.nih.gov/about/org/sacatm/meetings/docs/2016/september/videos/index.html>

⁹ National Toxicology Program website, SACATM Meeting videos. **Impediments to Adoption of Alternative Approaches,** Tim Malloy, UCLA, at 9:44

<https://ntp.niehs.nih.gov/about/org/sacatm/meetings/docs/2016/september/videos/index.html> and Malloy, T. (2016), Implementing the Vision for Toxicity Testing in the 21st Century: If You Build It, Will They Come? *Presentation to the Scientific Advisory Committee on Alternative Toxicological Methods*, 27th September 27, 2016

http://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2016/september/presentations/malloy_vision_fortoxtest_508.pdf

- suggested by CRS in their comments to FDA.¹⁰
- Dr. Lawrence Michak, 3M Center, SACATM Member: “Biggest impediment, first is regulatory acceptance.”¹¹
- Dr. William Janzen, Epizyme, Inc., SACATM Chair: “One of the key things discussed today, over and over, is regulation.”¹²

With the recent documented failure of animal-based preclinical test methods to predict safety in humans, it is more urgent than ever that FDA update regulations to broaden drug sponsors’ options to use the most predictive tests available.

Agency Guidance on the Use of the Draize test for Skin and Eye Irritation in Pharmaceutical Development

In late 2015, FDA issued narrow guidance to industry, stating the Draize test was no longer recommended in some circumstances and that in vitro or ex vivo testing would satisfy regulatory requirements in those cases.¹³ While this is an important step forward in communicating irritation testing requirements with sponsors, the guidance does not go far enough. It is limited in scope, and merely covers reformulated products and new routes of administration.

Last year, a coalition¹⁴ led by CRS and SMT submitted a citizen petition urging FDA to issue broad guidance communicating clearly with drug and device sponsors that the Draize rabbit test for skin and eye irritation is no longer required and that human relevant in vitro tests will be accepted. To assist FDA with this request, CRS submitted proposed draft guidance. FDA issued a preliminary response to the citizen petition,

¹⁰ National Toxicology Program website, SACATM Meeting videos. **Impediments to Adoption of Alternative Approaches**, Katherine Willett, HSUS, at 32:17
<https://ntp.niehs.nih.gov/about/org/sacatm/meetings/docs/2016/september/videos/index.html>

¹¹ National Toxicology Program website, SACATM Meeting videos. **Impediments to Adoption of Alternative Approaches**, Dr. Lawrence Michak, 3M Center at 37:04
<https://ntp.niehs.nih.gov/about/org/sacatm/meetings/docs/2016/september/videos/index.html>

¹² National Toxicology Program website, SACATM Meeting videos. **Next Steps Toward Developing a Strategy for Implementing the Vision for Toxicity Testing in the 21st Century**, Dr. William Janzen, Epizyme, Inc., SACATM Chair at 5:18
<https://ntp.niehs.nih.gov/about/org/sacatm/meetings/docs/2016/september/videos/index.html>

¹³ *Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route, Guidance for Industry and Review Staff, Good Review Practice*, October 2015.
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079245.pdf>

¹⁴ Petitioners: Center for Responsible Science, Safer Medicines Trust, MatTek and Invitro International

stating that due to limited resources, issuing guidance for skin and eye irritation was not among their numerous priorities.¹⁵

It is our sincere hope that FDA will issue broad guidance regarding acceptable methods for skin and eye irritation for topically applied products.

We appreciate the opportunity to submit these comments. We look forward to continued progress and collaboration.

Sincerely,



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¹⁵ FDA Docket # FDA-2016-P-1314, Requests FDA to issue guidance for industry on acceptable skin and eye irritation testing. <https://www.regulations.gov/docket?D=FDA-2016-P-1314>