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Sent via email to wolfe@niehs.nih.gov and Robbin Guy guyr2@niehs.nih.gov

Re: Public Comments for the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) annual meeting

Dear Dr. Wolfe:

The following comments are submitted on behalf of Center for Responsible Science (CRS). We appreciate the opportunity to submit these written comments and participate in the discussion regarding a strategy for implementing the US Strategic Roadmap: New Approaches to Evaluate the Safety of Chemicals and Medical Products. We applaud the efforts of all involved in developing this crucial strategy.

CRS promotes advances in regulatory science including the use of modern, effective preclinical test methods to streamline drug development and bring safer, more effective products to market more quickly at less cost. Our comments will focus on the need for updated regulations for drug development.

Strategic Goal 3: Encourage the adoption and use of new methods and approaches by federal agencies and regulated industries.

As noted in our 2016 SACATM comments, decades-old 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 and thirteen additional patient advocacy groups, technology developers and non-profit organizations¹ petitioned FDA² in July 2015 to update twenty-nine regulations to allow the use of the preclinical test method most predictive of human response. Under the proposed regulatory amendments, traditional testing would still be required in the absence of a scientifically recognized modern test method and would still be completely within the sponsors' discretion for use. Where a scientifically recognized modern test method exists for a particular purpose, sponsors would have the option to use the traditional method and/or the modern method. Petitioners merely seek an acknowledgment of regulatory acceptance of modern test methods in appropriate circumstances. Adoption of these conservative regulatory amendments would be an important first-step in moving forward.

FDA Commissioner Scott Gottlieb recently stated:

“FDA’s goal is to make sure that our policies are as scientifically advanced as the products we’re being asked to evaluate. We need to make certain our principles for regulation allow and facilitate beneficial new innovation while making sure that FDA continues to meet its gold standard for safety and effectiveness.”³

To achieve this goal, FDA must update regulations to allow for the use of the test most predictive of human response. We urge FDA to improve its “gold standard for safety and effectiveness” by updating regulations as requested in CRS’ Citizen Petition. The existing regulations contradict current FDA policy, promote the status quo and discourage innovation. Preclinical animal tests are required by FDA for new drugs and devices based on a presumption of human relevance and predictability, rather than robust scientific evidence.⁴ Considering the difficulties extrapolating preclinical animal data to human volunteers in clinical trials, FDA should promote the development and use of the test methods most predictive of human response. Updating IND and IDE regulations would help ensure its policies are as scientifically advanced as the products it evaluates.

¹ 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), Safer Medicines Trust, United Spinal Association, and 3D Biomatrix, Inc.

² 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>

³ US Food and Drug Administration, *Speech by Commissioner Gottlieb to Research America 2017 National Health Research Forum*, Research America 2017 National Health Research Forum, September 7, 2017, Washington, DC

<https://www.fda.gov/NewsEvents/Speeches/ucm575037.htm>

⁴ Bailey, J., Thew, M., Balls, M., *Predicting Human Drug Toxicity and Safety via Animal Tests: Can Any One Species Predict Drug Toxicity in Any Other, and Do Monkeys Help?*, ATLA 43, 393–403 (2015).

Additionally, 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. **CRS has documented 154 treatment related clinical trial deaths for the period of 2012 – 2017.**⁵ This number only reflects what has been reported in the media and some SEC filings. The actual number could be much higher and is unknown. **143 treatment-related deaths have occurred since January 2016.** It is time FDA brought IND and IDE regulations in line with stated policy to advance regulatory science and save lives of clinical trial participants and consumers.

The document developed for this meeting, *US Strategic Roadmap: New Approaches to Evaluate the Safety of Chemicals and Medical Products* discusses the importance of action on behalf of agencies:

“Federal agencies must take an active role in processes required for the successful adoption and use of NAMs, both within the federal government and internationally.

- Agencies should adopt clear language regarding the acceptance of NAMs. Industry stakeholders indicate that lack of clear guidance on the status of regulatory acceptance is a significant factor impeding the use of NAMs. Industries cannot be expected to start using new methods if they are uncertain about whether the data will be accepted by regulators. In order to facilitate use by industry, agencies should provide clear guidance on the use and acceptance of data from NAMs.”

While providing guidance to sponsors in pre-IND meetings and issuing formal guidance documents on NAMs is crucial, FDA needs to go further. Indeed, the usefulness of such guidance may be limited given that federal courts have interpreted FDA regulations, as currently written, to require traditional animal testing:

An IND is filed with the Food and Drug Administration after animal and laboratory studies have been completed.⁶

The FDA's Pre-Market Approval application requires manufacturers to submit extensive animal and human data to establish their devices' safety and effectiveness.⁷

Before issuing specific guidance on NAMs, FDA must modify current IND and IDE regulations that mandate the use of animal tests to allow for the use of the most predictive methodology.

⁵ See attached chart.

⁶ *Miller v. Pfizer, Inc.*, 196 F. Supp. 2d 1095, 1101 (D. Kan. 2002) (emphasis added).

⁷ *Reeves v. Acromed Corp.*, 44 F.3d 300, 303 (5th Cir. 1995) (emphasis added)

Once updated regulations are in place, any guidance issued on specific NAMs will be in line with regulations. Leaving current regulations in place while issuing guidance that contradicts regulations can only lead to confusion for drug and device sponsors.

Additionally, to encourage the use of NAMs agency submission reviewers must be educated and informed on available new technologies. Without reviewer education and uniform acceptance criteria, variability between reviewers' acceptance of new technologies will discourage their use and cause confusion for sponsors on their acceptability. Regular reviewer training and updated lists of available alternatives is crucial for early communication between regulators and sponsors on the acceptability of new test methods.

Conclusion

As *Archibald et al* point out: “In order to realize the potential of a human-based approach, we must continue to research and refine human based tests, improve and accelerate validation, educate researchers, regulators and insurers about the limitations of extrapolating between species and the advantages of a human-focused approach, clarify, pro-actively communicate and enforce official guidelines, and, most importantly, set timelines for action.”⁸

A crucial first step would be adoption of conservative regulation changes regarding drug and device development. We appreciate the opportunity to submit these comments. We look forward to continued progress and collaboration.

Sincerely,

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⁸ K. Archibald, T. Drake, R. Coleman, *Barriers to the Uptake of Human-based Test Methods, and How to Overcome Them*, ATLA 43, 301–308 (2015).

Clinical Trial Treatment-Related Deaths 2012-2015 – 11 + and 2016-2017 – 143+

Date	Drug/Company	Number of Deaths	Phase/Cause
8/12	Bristol-Myers Squibb BMS-986094	1	Phase II Cardiac
2014	Juno Therapeutics, Inc. Rocket Trial JCAR015	3	Phase I Cytokine Release Syndrome
2014	Juno Therapeutics, Inc. JCAR014 for Adult ALL	1	Cytokine Release Syndrome
2014	Novartis University of Pennsylvania CAR-T Study for Leukemia	3	Cytokine Release Syndrome and Sepsis
12/15	Zafgen Inc. – beloranib	2	Pulmonary emboli
2015	Juno Therapeutics Inc. JCAR014	1	Encephalopathy Cytokine Release Syndrome
1/17/16	BIA 10-2474 BIAL	1	Phase I unprecedented reaction in the brain
2016	Juno Therapeutics Inc. JCAR014 for Adult ALL	2	Cerebral Edema and CRS or neurotoxicity
2016	Juno Therapeutics Inc. JCAR014 for Lymphoma	1	CRS or neurotoxicity
2016	Juno Therapeutics Inc. JCAR014 for CLL	1	CRS, cerebral edema
2/16	CTI Biopharma Pacritinib	Unknown	Intracranial hemorrhage, cardiac failure, cardiac arrest
3/15/16	Gilead Sciences Zydelig	Multiple	Infections
May – June, 2016	Juno Therapeutics, Inc. Rocket Trial JCAR015	3	Phase II Cerebral Edema brought on by Cytokine Release Syndrome
6/26/16	Alnylam Pharmaceuticals givosiran	3	“early stage” hemorrhagic pancreatitis and

Date	Drug/Company	Number of Deaths	Phase/Cause
			pulmonary embolism
7/14/16	Ziopharm Oncology Ad-RTS-hIL-12	3	Phase I Intracranial hemorrhage (1) Other two deaths unknown
10/5/16	Alnylam Pharmaceuticals revusiran	17	Phase III Undisclosed cause of death
11/16	Juno Therapeutics, Inc. Rocket Trial JCAR015	2	Phase II Cerebral Edema brought on by Cytokine Release Syndrome
12/16	Seattle Genetics	4	Hepatotoxicity Phase II
12/16	Kite Pharma ZUMA-1 CAR-T	3	hemophagocytic lymphohistiocytosis, cardiac arrest in the setting of CRS and pulmonary embolism)
2017	Juno Therapeutics, Inc. Trascend Lymphoma Trial JCAR017	1	Diffuse alveolar damage
2/17	Stemline Therapeutics	4	Capillary Leak Syndrome Phase II
5/17	Kite Pharma ZUMA-1 CAR-T	1	Cerebral Edema brought on by Cytokine Release Syndrome
5/15/17	Ionis Pharmaceuticals – inotersen	1	Intracranial hemorrhage Phase III
6/13/17	Merck Keytruda Kenote- 183	29	Phase III myocarditis, Stevens- Johnson syndrome, myocardial infarction, pericardial

Date	Drug/Company	Number of Deaths	Phase/Cause
			hemorrhage, cardiac failure, respiratory tract infection, neutropenic sepsis, sepsis, multiple organ dysfunction, respiratory failure, and unknown.
6/13/17	Merck Keytruda Keynote-185	19	Phase III intestinal ischemia, cardio-respiratory arrest, suicide, pulmonary embolism, cardiac arrest, pneumonia, sudden death, myocarditis, large intestine perforation, and cardiac failure.
6/22/17	Seattle Genetics Vadastuximab talirine	Undisclosed	Undisclosed
Approved by FDA 2/17	Bristol-Myer Squibb nivolumab (Opdivo)	4	Unknown
Approved by FDA 4/17	Takeda – bigatinib ALUNBRIG	8	Phase II Pneumonia (2) Sudden death (1) Dyspnea (1) Respiratory Failure (1) Pulmonary embolism(1) Bacterial meningitis (1) Urosepsis (1)
8/2/17 (FDA voted against approval)	Johnson & Johnson sirukumab	34	All phases Cardiovascular events (13) Serious infections (8) Malignancies (6) Other (9)
9/4/17 FDA issues clinical	Collectis UCART123	1	Phase I Cytokine release

Date	Drug/Company	Number of Deaths	Phase/Cause
hold			syndrome and capillary leak syndrome
9/7/17	Alnylam Pharmaceuticals Fitusiran for hemophilia A and B	1	Mid-stage Blood clot cerebral venous sinus thrombosis (CVST)

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