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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.

ICCVAM was formed "To establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness."¹ Our comments will focus on the need for updated agency regulations and guidance to promote innovation and use of modern test methods.

Advancing Innovation and use of Human-Relevant Test Methods through ICCVAM Member Agency Regulation Updates

"The regulation of drugs can either grease the wheels of progress or throw a wrench in the works" concludes former Food and Drug Administration (FDA) Commissioner, Dr. Margaret Hamburg and former National Institute of Health (NIH) Director Dr. Elias

¹ ICCVAM Authorization Act, 42 U.S.C. 285I-3

Zerhouni.² Regulatory updates regarding preclinical test methods would advance the former.

A barrier to progress relates to perceived regulatory requirements. 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.

FDA's Investigational New Drug (IND) and Investigational Device Exemption (IDE) regulations give FDA the flexibility to accept non-animal test methods (NATMs), such as in vitro studies or prior experience with the drug or biological product in humans, when appropriate.³ However, despite this stated willingness to accept NATMs when they are at least as valid as other methods, FDA has not modified the text of its regulations. The current regulations clearly suggest a requirement for animal testing. For example:

- New Drug Application (NDA) Records and Reports: "To acquire necessary data for determining the safety and effectiveness of long-term use of such drugs, extensive animal and clinical tests are required as a condition of approval."⁴
- (Early Consultation on IND) Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials The purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing.⁵
- Application Technical Sections: "A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the animal pharmacology and toxicology data".⁶

The fact that companies perceive the full repertoire of animal tests as being required by the regulators, even if this is not always the case, discourages their adoption of NATMs, which are viewed as an additional and inessential expense.

To address the above, CRS, SMT and twelve additional patient advocacy groups, technology developers and non-profit organizations⁷ petitioned FDA⁸ last summer to

² *The need for global regulatory harmonization: A public health imperative*, E. Zerhouni and M. Hamburg, *Science Translational Medicine*, 11 May 2016:Vol. 8, Issue 338, pp. 338ed6
<http://stm.sciencemag.org/content/8/338/338ed6>

³ Letter from David H. Dorsey, Acting Deputy Commissioner for Policy, Planning and Budget, Food and Drugs to Katherine Meyer, Meyer Glitzenstein & Crystal 3-4 (May 20, 2010), available at <http://www.regulations.gov/#!documentDetail;D=FDA-2007-P-0109-0012>

⁴ 21 C.F.R. § 312.23(a)(3)(iv) (emphasis added)

⁵ 21 C.F.R. § 312.82(a) (emphasis added).

⁶ 21 C.F.R. § 314.50(d)(5)(i) (emphasis added)

⁷ Asterand Bioscience, AxoSim Technologies LLC, Empiriko, Friends of Cancer Research, HµREL® Corporation, In Vitro ADMET Laboratories, Invitro Cue, InVitro International, MatTek

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.

The twenty-nine FDA regulations facially require traditional animal testing and 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 promote efficiency and sponsor use of existing modern test methods and to signal further development to advance modernization of preclinical testing. The requested regulatory amendments would clear up any confusion, broaden testing options for sponsors, and spark innovation of more predictive methods.

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. 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. These updates will legally establish the acceptability of scientifically recognized modern and emerging test methods to support a medical product submission.

- On March 15th, six clinical trials on a cancer drug (idelalisib) were halted because of serious adverse events, including several deaths⁹. This followed the FDA's termination of a phase III trial in February of a blood cancer drug (Pacritinib) after patients died from "intracranial hemorrhage, cardiac failure and cardiac arrest."¹⁰

Corporation, NORD (National Organization for Rare Disorders), United Spinal Association, and 3D Biomatrix, Inc.

⁸ 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>

⁹ FDA Alerts Healthcare Professionals About Clinical Trials with Zydelig (idelalisib) in Combination with other Cancer Medicines, FDA website, March 15, 2016 http://www.fda.gov/Drugs/DrugSafety/ucm490618.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

¹⁰ *FDA Halts trial of Cancer drug by Seattle's CTI BioPharma after patient dies*. February 11, 2016 <http://www.seattletimes.com/business/fda-halts-cti-biopharma-drug-trial-for-detrimental-effect-on-survival/>

- In January, a previously healthy man participating in a clinical trial in France died and five others were hospitalized due to severe adverse reactions, including brain damage.¹¹ The drug had undergone preclinical tests in four species of animals before first-in-human tests¹². *Even with doses 400 times stronger than those given to the human volunteers, no adverse effects were noted in the animals.*¹³ The trial was conducted in “full compliance with worldwide regulations,”¹⁴ which further underscores the urgency for new regulations.
- In December 2015, a clinical trial participant died from bilateral pulmonary emboli, two months after FDA temporarily halted part of the clinical trial (Zafgen) due to the previous death of a 23 year-old clinical trial volunteer¹⁵.
- In August of 2012, Bristol-Myers Squibb discontinued development of a potential hepatitis C drug after nine participants in a phase II clinical trial of the therapy were hospitalized and one died¹⁶.

These tragedies echo an event in 2006 when six healthy men suffered multiple organ failure during testing of an arthritis and cancer drug candidate called TGN1412, even with a dose *500 times smaller than the dose found safe in preclinical animal studies*¹⁷.

Further tests performed by officials showed that in vitro testing using human cells could have predicted the danger that TGN1412 posed to humans, which the animal tests failed to predict¹⁸.

As *Archibald et al* point out: “On the question of human in vivo testing, it is widely held to be unethical to use humans as experimental subjects in the assessment of new

¹¹ Nano News, *Nothing to justify stopping clinical trials, says French health minister*, January 25, 2016 <http://nanonews.org/nothing-to-justify-stopping-clinical-trials-says-french/>

¹² The Guardian, *Man who died in French drug trial had ‘unprecedented’ reaction, say experts*, May 7, 2016. <https://www.theguardian.com/science/2016/mar/07/french-drug-trial-man-dead-expert-report-unprecedented-reaction>

¹³ *Id.*

¹⁴ Nano News, *supra* at 11.

¹⁵ *Zafgen Says a Second Patient Died in Beloranib Study*, The Wall Street Journal, December 2, 2015.

<http://www.wsj.com/articles/zafgen-says-another-patient-dies-in-beloranib-study-1449059965>

¹⁶ *Hepatitis C Drug trial halted after patient death*, Nature.com News Blog August 24, 2012 <http://blogs.nature.com/news/2012/08/hepatitis-c-drug-trial-halted-after-patient-death.html>

¹⁷ H. Attarwala, *TGN1412: From Discovery to Disaster*, J Young Pharm. 2010 Jul-Sep; 2(3): 332–336. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2964774/>

¹⁸ Expert Scientific Group on Phase I Clinical Trials, Final Report, 11/20/06, http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_073165.pdf

medicine safety and efficacy. However, we must recognize that we are in fact doing exactly that. It is established that in excess of 90% of potential medicines that have successfully passed the preclinical testing process fail, on the basis of safety and/or efficacy, when evaluated in human subjects. It is clear that human subjects, be they healthy volunteers or patients, are currently the most powerful contributors to the identification of clinical suitability. The obvious failure of animal-based preclinical testing to ‘weed out’ the unsuitable leaves the eventual human recipient as the real arbiter on this issue. If we cannot do any better than this, then we must acknowledge the key role human subjects play in the process, and consider how best to minimize the possibility of harm to them.”¹⁹

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

Since 2005, FDA has informally stated that Draize test data are not required for primary skin and eye irritation testing, but drug sponsors continue to provide Draize test data²⁰ - despite the prevalence of other primary skin and eye irritation methods that are more predictive.

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.²¹ 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.

A coalition²² led by CRS and SMT has 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 has submitted

¹⁹ 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).

²⁰ *Id.*

²¹ *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>

²² Petitioners: Center for Responsible Science, Safer Medicines Trust, MatTek and Invitro International

proposed draft guidance. 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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