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CITIZEN PETITION

The undersigned submit this petition under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq., and the Administrative Procedure Act, 5 U.S.C. § 553(e), to request the Commissioner of Food and Drugs (“Commissioner”) take action to clarify the regulatory pathway for the development and approval of drugs; ensure proper implementation of the Federal Food, Drug, and Cosmetic Act and the Food and Drug Omnibus Reform Act of 2022; and bring the agency’s regulatory directives and guidance documents in line with its admirable commitment to the promotion and development of new alternative methods (“NAMs”). Specifically, Petitioners request that the Commissioner amend current regulations that misleadingly suggest animal tests may be required for drug approval when they are not, issue a new guidance document listing and detailing the NAMs accepted by the agency for the approval of drugs for use by the regulated community, and include a directive regarding the agency’s acceptance of NAMs on all relevant current and future guidance documents.

These actions will clarify rules for the regulated community, potentially saving time and money in the development of new drugs; promote the use of the best available science to bring safe and effective drugs to the American people; and bring the agency’s regulatory landscape in line with its publicly stated goals and initiatives to reduce unnecessary, overly burdensome, and expensive animal testing. The changes requested in this petition will not *require* the use of one test method over another, but rather are intended to make clear to the regulated community the complete range of types of data accepted by the agency for the purposes of approving the use and marketing of drugs.

This petition is submitted on behalf of the Humane Society of the United States and the Humane Society Legislative Fund (collectively, “Petitioners”). The Humane Society of the United States (“HSUS”) is a non-profit animal protection organization founded in 1954 and headquartered in Washington, D.C. Together with its affiliates, the HSUS has regional offices and direct animal care facilities located throughout the country. The HSUS actively works (through public education, investigation, litigation, legislation, and advocacy) to combat animal abuse and exploitation and to promote the protection and welfare of all animals, including animals used in research, testing, and training. The Humane Society Legislative Fund (“HSLF”) is a social welfare organization incorporated under section 501(c)(4) of the

Internal Revenue Code and formed in 2004 as a separate lobbying affiliate of the HSUS. HSLF works to pass animal protection laws at the state and federal levels. HSLF works to ensure that animals have a voice before lawmakers by advocating for measures to eliminate animal cruelty and suffering and by educating the public on animal protection issues. Among other issues, HSLF advocates against unnecessary and inhumane practices used in animal testing and research, and for non-animal methods and strategies that end new animal testing.

A. ACTION REQUESTED

Pursuant to the Administrative Procedure Act, 5 U.S.C. § 553(e), this petition respectfully requests that the Commissioner take action consistent with Congress' enactment of the Federal Food, Drug, and Cosmetic Act ("FDCA") and the Food and Drug Omnibus Reform Act of 2022 ("FDORA") and amend its regulations and guidance documents to clarify the requirements for approval of drugs for the benefit of the regulated community, including the acceptance of data from new alternative methods ("NAMs"). Specifically, Petitioners request three categories of action. First, Petitioners request that the Commissioner revise Food and Drug Administration ("FDA") regulations that may be read to require in vivo animal tests for the approval of drugs. See Section A(1) (detailing requested revisions). Second, Petitioners request that the Commissioner issue (and regularly update) a new guidance document that provides specific up-to-date information to the regulated community regarding the NAMs that the agency accepts in lieu of nonhuman vertebrate test methods for the development and approval of drugs. See Section A(2). Third, Petitioners request that the Commissioner undertake a broader project to update the agency's guidance documents, many of which are outdated by several decades, to explicitly acknowledge FDA's acceptance of data from NAMs and encourage sponsors to refer to the new NAMs guidance document before embarking on any new animal studies. See Section A(3).

1. Revise FDA Regulations That Suggest Animal Testing is Required

Petitioners respectfully request the following revisions to current FDA regulations in order to clarify the regulatory requirements for drugs to the regulated community. All proposed changes are in **bold red text**; proposed additions are underlined, and proposed deletions are **stricken**.

a. *21 C.F.R. § 312.3 (Investigational New Drug Application: Definitions and interpretations.)*

"Marketing application means an application for a new drug submitted under section 505(b) of the act or a biologics license application for a biological product submitted under the Public Health Service Act.

Nonclinical test or study means a test or study conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test, that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug. Such test may include the following: (1) Cell-based assays. (2) Organ chips and microphysiological systems. (3) Computer modeling. (4) Other nonhuman or human biology-based test methods, such as bioprinting. (5) Animal tests. Nonclinical data means data derived from a nonclinical test or study.

Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual

that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.”

- b. 21 C.F.R. § 312.22(c) (*Investigational New Drug Application: General principles of the IND submission.*)

“The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of **nonclinical animal** toxicology studies or other human studies as appropriate . . .”

- c. 21 C.F.R. § 312.23(a)(3)(iv) (*Investigational New Drug Application: IND content and format.*)

“A brief description of the overall plan for investigating the drug product for the following year. The plan should include . . . (f) any risks of particular severity or seriousness anticipated on the basis of **the** toxicological data **from nonclinical tests in animals** or prior studies in humans with the drug or related drugs.”

- d. 21 C.F.R. § 312.23(a)(5)(ii) (*Investigational New Drug Application: IND content and format.*)

“A summary of the pharmacological and toxicological effects of the drug **based on nonclinical tests in animals**, and, to the extent known, in humans.”

- e. 21 C.F.R. § 312.23(a)(5)(iii) (*Investigational New Drug Application: IND content and format.*)

“A summary of the pharmacokinetics and biological disposition of the drug in **nonclinical tests animals** and, if known, in humans.”

- f. 21 C.F.R. § 312.23(a)(8) (*Investigational New Drug Application: IND content and format.*)

“Pharmacology and toxicology information. Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of **nonclinical animal and other** tests required varies with the duration and nature of the proposed clinical investigations. Guidance documents are available from FDA that describe ways in which these requirements may be met. Such information is required to include the identification and qualifications of the individuals who evaluated the results of such studies and concluded that it is reasonably safe to begin the proposed investigations and a statement of where the investigations were conducted and where the records are available for inspection. As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety.”

- g. 21 C.F.R. § 312.23(a)(8)(i) (*Investigational New Drug Application: IND content and format.*)

“Pharmacology and drug disposition. A section describing the pharmacological effects and mechanism(s) of action of the drug **based on nonclinical tests in animals**, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.”

- h. 21 C.F.R. § 312.23(a)(8)(ii) (*Investigational New Drug Application: IND content and format.*)
“Toxicology. (a) An integrated summary of the toxicological effects of the drug in **nonclinical tests animals and in vitro**. Depending on the nature of the drug and the phase of the investigation, the description **may is to** include the results of acute, subacute, and chronic toxicity tests; **preclinical nonclinical** tests of the drug’s effects on reproduction and the developing fetus; any special toxicity test related to the drug’s particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); **or and** any **nonclinical in vitro** studies intended to evaluate drug toxicity.”
- i. 21 C.F.R. § 312.23(a)(10)(i) (*Investigational New Drug Application: IND content and format.*)
“Drug dependence and abuse potential. If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and **nonclinical experience and studies in test animals**.”
- j. 21 C.F.R. § 312.23(a)(10)(ii) (*Investigational New Drug Application: IND content and format.*)
“Radioactive drugs. If the drug is a radioactive drug, sufficient data from **nonclinical animal** or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject . . .”
- k. 21 C.F.R. § 312.33(b)(6) (*Investigational New Drug Application: Annual reports.*)
“A list of the **nonpreclinical** studies (**including animal studies**) completed or in progress during the past year and a summary of the major **nonpreclinical** findings.”
- l. 21 C.F.R. § 312.82(a) (*Investigational New Drug Application: Early consultation.*)
“Pre-investigational new drug (IND) meetings. Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of **nonclinical animal** studies needed to initiate human testing . . .”
- m. 21 C.F.R. § 312.88 (*Investigational New Drug Application: Safeguards for patient safety.*)
“All of the safeguards incorporated within Parts 50, 56, 312, 314, and 600 of this chapter designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section . . . These safeguards further include the review of **nonclinical animal** studies prior to initial human testing . . .”
- n. 21 C.F.R. § 314.3 (*Applications for FDA Approval to Market a New Drug: Definitions.*)
“Newly acquired information is data, analyses, or other information not previously submitted to the Agency, which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

Nonclinical test or study means a test or study conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test, that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug. Such test may include the following: (1) Cell-based assays. (2) Organ chips and microphysiological systems. (3) Computer modeling. (4) Other nonhuman or human biology-based test methods, such as bioprinting. (5) Animal tests. Nonclinical data means data derived from a nonclinical test or study.

Original application or original NDA is a pending NDA for which FDA has never issued a complete response letter or approval letter, or an NDA that was submitted again after FDA had refused to file it or after it was withdrawn without being approved.”

- o. 21 C.F.R. § 314.50(d)(2) (*Applications for FDA Approval to Market a New Drug: Content and format of an NDA.*)

“Nonclinical pharmacology and toxicology section. A section describing, with the aid of graphs and tables, **any applicable nonclinical animal and in vitro** studies with drug . . .”

- p. 21 C.F.R. § 314.50(d)(2)(iv) (*Applications for FDA Approval to Market a New Drug: Content and format of an NDA.*)

“Any studies of the absorption, distribution, metabolism, and excretion of the drug in **nonclinical tests animals.**”

- q. 21 C.F.R. § 314.50(d)(5)(i) (*Applications for FDA Approval to Market a New Drug: Content and format of an NDA.*)

“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 **nonclinical animal** pharmacology and toxicology data.”

- r. 21 C.F.R. § 314.50(d)(5)(vi)(a) (*Applications for FDA Approval to Market a New Drug: Content and format of an NDA.*)

“(a) The applicant must submit an integrated summary of all available information about the safety of the drug product, including pertinent **nonclinical animal** data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations . . .”

- s. 21 C.F.R. § 314.50(d)(5)(vi)(b) (*Applications for FDA Approval to Market a New Drug: Content and format of an NDA.*)

“(b) The applicant must, under section 505(i) of the act, update periodically its pending application with new safety information learned about the drug These ‘safety update reports’ are required to include the same kinds of information (from clinical studies, **nonclinical animal** studies, **or and** other sources) and are required to be submitted in the same format . . .”

- t. 21 C.F.R. § 314.200(d)(3)(1)(A) (Applications for FDA Approval to Market a New Drug: Notice of opportunity for hearing; notice of participation and request for hearing; grant or denial of hearing.)

“ . . . the following format.

I. Safety data.

A. **Nonclinical Animal** safety data.”

- u. 21 C.F.R. § 314.610 (Applications for FDA Approval to Market a New Drug: Approval based on evidence of effectiveness from **nonclinical studies in animals**.)

“(a) FDA may grant marketing approval for a new drug product for which safety has been established and for which the requirements of § 314.600 are met based on adequate and well-controlled **nonclinical animal** studies when the results of those **nonclinical animal** studies establish that the drug product is reasonably likely to produce clinical benefit in humans. In assessing the sufficiency of **nonclinical animal** data, the agency may take into account other data, including human data, available to the agency. FDA will rely on the evidence from **nonclinical studies in animals** to provide substantial evidence of the effectiveness of these products only when:

(1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;

(2) The effect is demonstrated in more than one **nonclinical test animal species** expected to react with a response predictive for humans, unless the effect is demonstrated in a single **nonclinical test animal species** that represents a sufficiently well-characterized **animal** model for predicting the response in humans;

(3) The **nonclinical animal** study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and

(4) The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in **nonclinical tests animals** and humans, allows selection of an effective dose in humans . . .

(b)(3) . . . The patient labeling must explain that, for ethical or feasibility reasons, the drug’s approval was based on efficacy studies **not** conducted in **humans animals-alone** . . .”

- v. 21 C.F.R. § 315.2 (Diagnostic Radiopharmaceuticals: Definitions.)

“For purposes of this part:

Diagnostic radiopharmaceutical means:

(a) An article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or

(b) Any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such article as defined in paragraph (a) of this section.

Nonclinical test or study means a test or study conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test, that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug. Such test may include the following:

(1) Cell-based assays. (2) Organ chips and microphysiological systems. (3) Computer modeling. (4) Other nonhuman or human biology-based test methods, such as bioprinting. (5) Animal tests. Nonclinical data means data derived from a nonclinical test or study.”

w. 21 C.F.R. § 315.6(d) (*Diagnostic Radiopharmaceuticals: Evaluation of safety.*)

“Radiation safety assessment. The radiation safety assessment must establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate nonclinical tests animal models. The maximum tolerated dose need not be established.”

x. 21 C.F.R. § 316.3 (*Orphan Drugs: Definitions.*)

“(9) Marketing application means an application for approval of a new drug filed under section 505(b) of the act or an application for a biologics license submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

(10) Nonclinical test or study means a test or study conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test, that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug. Such test may include the following: (i) Cell-based assays. (ii) Organ chips and microphysiological systems. (iii) Computer modeling. (iv) Other nonhuman or human biology-based test methods, such as bioprinting. (v) Animal tests. Nonclinical data means data derived from a nonclinical test or study.

~~(11)~~(10) Orphan drug means a drug intended for use in a rare disease or condition as defined in section 526 of the act.

~~(12)~~(11) Orphan-drug designation means FDA’s act of granting a request for designation under section 526 of the act.

~~(13)~~(12) Orphan-drug exclusive approval or exclusive approval means that, effective on the date of FDA approval as stated in the approval letter of a marketing application for a sponsor of a designated orphan drug, no approval will be given to a subsequent sponsor of the same drug for the same use or indication for 7 years, except as otherwise provided by law or in this part. A designated drug will receive orphan-drug exclusive approval only if the same drug has not already been approved for the same use or indication.

~~(14)~~(13) Orphan subset of a non-rare disease or condition (“orphan subset”) means that use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but use of the drug outside of that subset (in the remaining persons with the non-rare disease or condition) would be inappropriate owing to some property(ies) of the drug, for example, drug toxicity, mechanism of action, or previous clinical experience with the drug.

~~(15)~~(14) Same drug means:

(i) If it is a drug composed of small molecules, a drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or

other noncovalent derivative such as a complex, chelate or clathrate has not been previously approved, except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.

(ii) If it is a drug composed of large molecules (macromolecules), a drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use as a previously approved drug, except that, if the subsequent drug can be shown to be clinically superior, it will not be considered to be the same drug. This criterion will be applied as follows to different kinds of macromolecules:

(A) Two protein drugs would be considered the same if the only differences in structure between them were due to post-translational events or infidelity of translation or transcription or were minor differences in amino acid sequence; other potentially important differences, such as different glycosylation patterns or different tertiary structures, would not cause the drugs to be considered different unless the differences were shown to be clinically superior.

(B) Two polysaccharide drugs would be considered the same if they had identical saccharide repeating units, even if the number of units were to vary and even if there were postpolymerization modifications, unless the subsequent drug could be shown to be clinically superior.

(C) Two polynucleotide drugs consisting of two or more distinct nucleotides would be considered the same if they had an identical sequence of purine and pyrimidine bases (or their derivatives) bound to an identical sugar backbone (ribose, deoxyribose, or modifications of these sugars), unless the subsequent drug were shown to be clinically superior.

(D) Closely related, complex partly definable drugs with similar therapeutic intent, such as two live viral vaccines for the same indication, would be considered the same unless the subsequent drug was shown to be clinically superior.

(16) (15) Sponsor means the entity that assumes responsibility for a clinical or nonclinical investigation of a drug, including the responsibility for compliance with applicable provisions of the act and regulations. A sponsor may be an individual, partnership, corporation, or Government agency and may be a manufacturer, scientific institution, or an investigator regularly and lawfully engaged in the investigation of drugs. For purposes of the Orphan Drug Act, FDA considers the real party or parties in interest to be a sponsor.”

- y. 21 C.F.R. § 316.20(b)(4) (*Orphan Drugs: Content and format of a request for orphan-drug designation.*)

“ . . . including all relevant data from **nonclinical tests, including** in vitro laboratory studies, **preclinical nonclinical** efficacy studies conducted in an animal **or other** models for the human disease or condition, and clinical experience with the drug in the rare disease or condition that are available to the sponsor, whether positive, negative, or inconclusive. Animal toxicology studies are generally not relevant to a request for orphan-drug designation.”

- z. 21 C.F.R. § 330.1 (*Over-the-Counter (OTC) Human Drugs Which Are Generally Recognized as Safe and Effective and Not Misbranded: General conditions for general recognition as safe, effective and not misbranded.*)

“(k) For purposes of this section, nonclinical test or study means a test or study conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test, that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug. Such test

may include the following: (1) Cell-based assays. (2) Organ chips and microphysiological systems. (3) Computer modeling. (4) Other nonhuman or human biology-based test methods, such as bioprinting. (5) Animal tests. Nonclinical data means data derived from a nonclinical test or study.”

- aa. 21 C.F.R. § 330.10(a)(2) (*Over-the-Counter (OTC) Human Drugs Which Are Generally Recognized as Safe and Effective and Not Misbranded: Procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs.*)

“Request for data and views. The Commissioner will publish a notice in the FEDERAL REGISTER requesting interested persons to submit, for review and evaluation by an advisory review panel . . . All submissions must be in the following format:

OTC DRUG REVIEW INFORMATION

I. Label(s) and all labeling (preferably mounted and filed with the other data -- facsimile labeling is acceptable in lieu of actual container labeling).

II. A statement setting forth the quantities of active ingredients of the drug.

III. **Nonclinical Animal** safety data . . .”

- bb. 21 C.F.R. § 330.14(j)(4)(iv) (*Over-the-Counter (OTC) Human Drugs Which Are Generally Recognized as Safe and Effective and Not Misbranded: Additional criteria and procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded.*)

“The submission does not contain an analysis and summary of the data and other supporting information, organized by clinical or nonclinical area, such as clinical efficacy data, clinical safety data, clinical pharmacology, adverse event reports, **nonclinical animal** toxicology, chemistry data, **or and** compendial status.”

- cc. 21 C.F.R. § 361.1(d)(7) (*Prescription Drugs for Human Use Generally Recognized as Safe and Effective and Not Misbranded: Drugs Used in Research: Radioactive drugs for certain research uses.*)

“Research protocol. No matter how small the amount of radioactivity, no study involving administration of a radioactive drug, as defined in § 310.3(n) of this chapter, to research subjects under this section, shall be permitted unless the Radioactive Drug Research Committee concludes, in its judgment, that scientific knowledge and benefit is likely to result from that study. Therefore, the protocol shall be based upon a sound rationale derived from appropriate **nonclinical animal** studies.”

- dd. 21 C.F.R. § 361.1 (*Prescription Drugs for Human Use Generally Recognized as Safe and Effective and Not Misbranded: Drugs Used in Research: Radioactive drugs for certain research uses.*)

“(g) For purposes of this section, nonclinical test or study means a test or study conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test, that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug. Such test may include the following: (1) Cell-based assays. (2) Organ chips and microphysiological systems. (3) Computer modeling. (4) Other nonhuman or human biology-based test

methods, such as bioprinting. (5) Animal tests. Nonclinical data means data derived from a nonclinical test or study.”

2. Issue a New Guidance Document Outlining the NAMs Accepted by the Agency

Petitioners request the Commissioner publish and continually update a new guidance document specifying the NAMs accepted for drug approvals by the agency (hereinafter, “NAMs Guidance Document”). This document should include all NAMs that have been accepted by the agency for drug approvals, as well as their defined contexts of use¹ and guidelines for the qualified methodology of each test. This information is readily available to FDA, but because it is not known or easily ascertainable by the regulated community, pharmaceutical companies are unable to rely on NAMs with a sufficient degree of confidence that the agency will accept that data in lieu of data from animal models. Petitioners further request that the agency continue to update the NAMs Guidance Document, as more NAMs are developed, relied on by the agency, and accepted for different contexts of use.²

Petitioners further request that the NAMs Guidance Document be presented in two sections, Tier 1 and Tier 2, based on the methods’ use of live animals. Tier 1 should encompass methods that do not require the use of any live animals, and sponsors should be encouraged to favor Tier 1 NAMs when available. Petitioners propose that the NAMs Guidance Document contain the following text:

In this Guidance Document, NAMs accepted by FDA are organized by prioritization of use as determined by FDA and in line with the principles of the 3Rs to replace, reduce, and refine the use of animals in testing. Tier 1 lists methods that do not rely on the use of live, intact nonhuman animals (vertebrate or invertebrate), including, but not limited to, in vitro methods (e.g. methods using cell lines, primary cells, organoid cultures, microphysiological systems, stem cells, animal cells, or animal tissues), in chemico methods (e.g. cell-free systems to measure reactivity), in silico methods (e.g. mathematical modeling of existing data sets, computational modeling), ex vivo methods (e.g. tissue slices, explant cultures), or human volunteers. Tier 2 lists methods that require the use of intact animals. Where live intact animals are used, the use of immature forms (e.g. embryos or larvae), amoebae, nematodes, or other ‘non-classical’ organisms should be prioritized.

¹ “Context of use” is used herein to mean a statement that fully and clearly describes the way the model is to be used and the purpose of the use.

² See, e.g., Frank R. Lautenberg Chemical Safety Act for the 21st Century Act, Pub. L. 114-182, § 4, 130 Stat. 452-454 (2016) (requiring the EPA to develop and implement its 2018 strategic plan to promote the development and implementation of alternative test methods and strategies to reduce, refine, or replace alternative methods in part by updating a publicly available list of alternative test methods acceptable for regulatory decision making); *Chemicals under the Toxic Substances Control Act (TSCA), Updates to the EPA List of Alternative Test Methods to Animal Testing*, U.S. ENVTL. AGENCY, <https://www.epa.gov/chemicals-under-tsca/updates-epa-list-alternative-test-methods-animal-testing> (last updated Apr. 10, 2024).

3. Update Existing Guidance Documents to Specifically Reference the New NAMs Guidance Document

Petitioners also request that existing and future guidance documents regarding the development and approval of drugs issued by FDA include a link and reference to the NAMs Guidance Document, so that regulated entities are made aware of the availability of and the agency's acceptance of NAMs. Petitioners propose that the following text and incorporation of the NAMs Guidance Document be included at the beginning of all current and future guidance documents regarding the development and approval of drugs.³

FDA supports the principles of the 3Rs to replace, reduce, and refine animal use in testing. We accept NAMs data for consideration as part of the drug review and approval process. To this end, sponsors are encouraged to consult and consider the agency's NAMs Guidance Document, which contains a list of alternative methods currently accepted by the agency, before undertaking any new animal studies.

Where sponsors wish to rely on a non-animal testing method that is not currently included in the NAMs Guidance Document, they are encouraged to consult with the agency.

B. STATEMENT OF GROUNDS

1. Factual Background

Each year, pharmaceutical companies in the United States spend somewhere between \$83 billion⁴ and \$101 billion⁵ on the research and development needed to bring new drugs to the American people. Bringing even one new drug to market is an extraordinarily costly venture; the average cost of development of a single new drug has risen to over \$2.2 billion, marking a 15% increase in only one year.⁶ This ever-increasing cost has resulted in the lowest recorded return on investment in the pharmaceutical industry: only about 1%.⁷

This astronomical initial expenditure, coupled with a remarkably low rate of return, has led to a marked decrease in incentives for the pharmaceutical industry to research, explore, develop, and bring to market new therapies. This hurts not only the United States pharmaceutical industry and economy overall, but

³ While some guidance documents already include a general statement about alternative test methods, these statements do not provide sufficiently specific directives or guidance regarding NAMs accepted by the agency to provide clarity to the regulated community. See, e.g., U.S. FOOD & DRUG ADMIN., ONCOLOGY THERAPEUTIC RADIOPHARMACEUTICALS: NONCLINICAL STUDIES AND LABELING RECOMMENDATIONS GUIDANCE FOR INDUSTRY (2019).

⁴ *Research and Development in the Pharmaceutical Industry*, CONG. BUDGET OFF. (Apr. 2021), <https://www.cbo.gov/publication/57126>.

⁵ *Research & Development Policy Framework*, PHARMA, <https://pharma.org/en/policy-issues/Research-and-Development-Policy-Framework> (last updated Jan. 22, 2024).

⁶ *Seize the Digital Momentum: Measuring the Return from Pharmaceutical Innovation 2022*, DELOITTE CTR. FOR HEALTH SOLS., 4 (Jan. 2023) [deloitte-uk-seize-digital-momentum-rd-roi-2022.pdf](https://www.deloitte-uk-seize-digital-momentum-rd-roi-2022.pdf).

⁷ Deloitte, *Deloitte's 13th Annual Pharmaceutical Innovation Report: Pharma R&D Return on Investment Falls in Post-Pandemic Market*, PR NEWswire (Feb. 6, 2023), <https://www.prnewswire.com/news-releases/deloittes-13th-annual-pharmaceutical-innovation-report-pharma-rd-return-on-investment-falls-in-post-pandemic-market-301738807.html>.

also the American people, who rely on the development of new drugs to treat a broad range of disorders and diseases, as well as efforts to address global health concerns.

Pre-clinical testing—the efforts to develop and qualify new therapies before they are studied in trials in humans—constitutes a significant portion of the cost of developing and bringing to market new drugs in the United States. A recent study from Johns Hopkins Bloomberg School of Public Health found that clinical studies—those conducted in patients after receiving FDA approval to do so—make up less than one percent of the cost of bringing a new drug to American consumers.⁸ Much of the rest of that money is spent on time-consuming, sometimes duplicative, and often unnecessary tests conducted on animals in laboratories. These tests can cost tens to hundreds of thousands of dollars, in addition to taking years to complete.

Non-animal test methods are often less expensive and time-consuming than many in vivo test methods.⁹ Most importantly, they are also more consistent and a more reliable predictor of both safety and efficacy in humans. These new alternative methods include cell-free assays to identify reactive compounds (in chemico methods), cell-based assays, microphysiological systems, organ chips (in vitro methods), and computer-modeling techniques (in silico methods). While these methods are already widely available (federal agencies already accept over 100 replacement, reduction, or refinement methods for the purposes of chemical safety testing, of which more than half are non-animal¹⁰), additional test methods and approaches are being developed and made available. This rapid development will only increase with additional funding, such as the recent \$6.5 million congressional appropriation for FDA’s New Alternative Methods Program.¹¹

2. Legal and Regulatory Background

a. *The Current Statutory and Regulatory Scheme*

The Food and Drug Administration (“FDA”) is the federal agency tasked with regulating the approval of drugs and therapies brought to American consumers. As part of this process, FDA reviews submissions of new drug applications (“NDAs”), which are based on human clinical data. In order to receive FDA approval to begin to conduct these trials in humans, pharmaceutical companies must submit an Investigational New Drug (“IND”) application. An IND application includes data derived from nonclinical testing, including any tests that were conducted on animals, as well as data from NAMs.

⁸ *Clinical Trials to Obtain FDA Approval Typically Account for Small Proportion of Total Drug Research and Development Costs, Study Suggests*, JOHNS HOPKINS BLOOMBERG SCH. OF PUB. HEALTH (Sept. 24, 2018), <https://publichealth.jhu.edu/2018/cost-of-clinical-trials-for-new-drug-fda-approval-are-fraction-of-total-tab>.

⁹ *Costs of Animal and Non-Animal Testing*, HUMANE SOCIETY INTERNATIONAL, https://www.hsi.org/news-resources/time_and_cost/ (last visited Apr. 22, 2024).

¹⁰ *Alternative Methods Accepted by US Agencies*, NAT’L TOXICOLOGY PROGRAM U.S. DEP’T OF HEALTH & HUM. SERV., <https://ntp.niehs.nih.gov/whatwestudy/niceatm/accept-methods> (last visited Apr. 22, 2024).

¹¹ AGRIC., RURAL DEV., FOOD & DRUG ADMIN., & RELATED AGENCIES, APPROPRIATIONS ACT, 2023, 117TH CONG. CONGRESSIONAL DIRECTIVES 49 (2023), <https://www.appropriations.senate.gov/imo/media/doc/Division%20A%20-%20Agriculture%20Statement%20FY23.pdf> (hereinafter “FY 2023 Joint Explanatory Statement”) (appropriating \$5,000,000 to be used to Reduce Animal Testing through Alternative Methods); AGRIC., RURAL DEV., FOOD & DRUG ADMIN., & RELATED AGENCIES, APPROPRIATIONS ACT, 118TH CONG. CONGRESSIONAL DIRECTIVES 30 (2024), [https://docs.house.gov/billsthisweek/20240304/FY24%20Ag%20Conference%20JES%20scan%203.2.24%20\(1\).pdf](https://docs.house.gov/billsthisweek/20240304/FY24%20Ag%20Conference%20JES%20scan%203.2.24%20(1).pdf) (hereinafter “FY 2024 Joint Explanatory Statement”) (appropriating \$1,500,000 to be used to Reduce Animal Testing through Alternative Methods).

The FDCA gives FDA the authority to oversee the safety of food, drugs, medical devices, and cosmetics. Section 505 of the FDCA establishes the requirements for the manufacture and marketing of drugs, including for the approval of new drugs.¹² A sponsor who wishes to market a new drug must file an application with the agency containing specific information, after which the agency has 180 days to respond.¹³ The FDCA does not explicitly require animal tests for drug approval.

FDA implements the requirements of the FDCA through regulations codified at Title 21 of the Code of Federal Regulations. Section 310 of these regulations governs the approval of new drugs,¹⁴ and Section 312 governs the application process for Investigational New Drugs, “including procedures and requirements for the submission to, and review by, the Food and Drug Administration of investigational new drug applications.”¹⁵ Section 314 governs the marketing of new drugs,¹⁶ and Sections 315 and 316 provide particularized regulation of diagnostic radiopharmaceuticals and orphan drugs.¹⁷ Sections 328 through 361 apply to over-the-counter drugs.¹⁸

FDA provides additional information about its drug regulatory and approval structure and processes to the regulated community via non-binding guidance documents, which are available on its website. These guidance documents include suggestions and recommendations for sponsors submitting INDs for different kinds of drugs—such as novel anti-infectives, inhaled drugs, and drugs for oncology—and different kinds of studies conducted for the purpose of IND submissions.

In 2022, Congress passed the FDORA.¹⁹ This legislation was intended to “allow for alternatives to animal testing for purposes of drug and biological product applications” and removed references to “tests on animals” and “animal tests” from the FDCA. The FDORA also amended the FDCA by defining the term “nonclinical test” as “a test conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test, that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug. Such tests may include the following: (1) Cell-based assays. (2) Organ chips and microphysiological systems. (3) Computer modeling. (4) Other nonhuman or human biology-based test methods, such as bioprinting. (5) Animal tests.”²⁰ While the FDCA already gave FDA broad discretion to accept NAMs, the FDORA underscored this authority and emphasized Congressional intent to remove any perception to the contrary.

¹² See 21 U.S.C. §§ 351-364j.

¹³ See *id.* § 355.

¹⁴ *Id.* §§ 310.3-310.548.

¹⁵ *Id.* §§ 312.1-312.320.

¹⁶ *Id.* §§ 314.1-314.650.

¹⁷ *Id.* §§ 315.1-316.52.

¹⁸ *Id.* §§ 328.1-369.21.

¹⁹ Consolidated Appropriations Act of 2023, Pub. L. No. 117-328, 136 Stat. 5821-5822 (2022) (noting that the FDORA passed as part of the Consolidated Appropriations Act and included language from S.5002, 117th Cong (2022), co-authored by Senators Cory Booker (D-NJ) and Rand Paul (R-KY) and Representatives Buchanan (R-FL) and Luria (D-VA) entitled the FDA Modernization Act 2.0).

²⁰ 21 U.S.C. § 355(z).

b. *Congressional Calls for the Prioritization of Non-Animal Test Methods*

Congress has continually supported the development, acceptance, and use of alternative, non-animal test methods across multiple federal agencies, including FDA. In 1993, Congress passed the National Institutes of Health Revitalization Act, which directed the National Institute of Environmental Health Sciences (“NIEHS”) to “develop and validate assays and protocols, including alternative methods that can reduce or eliminate the use of animals in acute or chronic safety testing” and “establish criteria for the validation and regulatory acceptance of alternative testing.”²¹ In order to fulfill this mandate, in 1994 NIEHS established what was then intended to be a temporary committee, comprised of representatives from 15 federal agencies, known as the Interagency Coordinating Committee on the Validation of Alternative Methods (“ICCVAM”).²²

Six years later, the ICCVAM Authorization Act of 2000 was signed into law, codifying the permanent existence of ICCVAM.²³ The law set forth objectives of increasing the efficiency of federal test method review and reducing animal testing where feasible. Specifically, it requires member agencies to “*promote and encourage the development and use of alternatives to animal test methods.*”²⁴ FDA was an original member agency of ICCVAM in 1994, has held the chair, and has played an active role in the review of ICCVAM-validated alternative test methods. Several alternative methods that replace, reduce, or refine animal use have been validated through ICCVAM including for FDA regulated products.

In 2016, the Frank R. Lautenberg Chemical Safety for the 21st Century Act was signed into law, updating the decades-old Toxic Substances Control Act (“TSCA”) and directing the Environmental Protection Agency (“EPA”) to reduce and replace the use of vertebrate animals in the testing of chemical substances or mixtures and promote the development and incorporation of alternative methods that do not require new vertebrate animal testing.²⁵ It was the first-of-its kind law in the United States, with Congress specifying that animal testing should only be undertaken as a last resort.

Congress has also supported the advancement of alternative testing methods through appropriations language and funding. The Fiscal Year 2023 budget provided \$5 million in new funding to develop and support the New Alternative Methods Program,²⁶ a cross-agency program requested by the administration to “spur the adoption of new alternative methods for regulatory use that can replace, reduce and refine animal testing.”²⁷ In Fiscal Year 2024, Congress increased the funding for the New Alternative Methods Program by providing \$6.5 million in funding.²⁸ Report language from both the House of Representatives and Senate directed FDA to “efficiently and expeditiously use existing funds to

²¹ National Institutes of Health Revitalization Act of 1993, Pub. L. No. 103-43, § 1301, 107 Stat. 122.

²² Notice of Availability, A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods, 62 Fed. Reg. 11901 (1997).

²³ ICCVAM Authorization Act of 2000, Pub. L. No. 106-545, § 4, 114 Stat. 2721.

²⁴ *Id.* (emphasis added).

²⁵ Frank R. Lautenberg Chemical Safety Act for the 21st Century Act § 4, 130 Stat. 452-454.

²⁶ FY 2023 Joint Explanatory Statement.

²⁷ NAT’L INSTIT. OF HEALTH, CONGRESSIONAL JUSTIFICATION FISCAL YEAR 2023 24 (2022).

²⁸ FY 2024 Joint Explanatory Statement.

reduce animal testing and advance alternative methods in a measurable and impactful way” and requested a status report on FDA’s New Alternative Methods Program.²⁹

In December 2022, President Biden signed the Consolidated Appropriations Act, 2023, which contains the FDORA.³⁰ The FDORA amended Section 505 of the FDCA by defining the term “nonclinical test” to include cell-based assays, organ chips and microphysiological systems, computer modeling, other nonhuman or human biology-based test methods, and animal tests, providing absolute clarity that the FDCA does not require animal tests for evaluating the safety and efficacy of drugs.³¹

c. *FDA’s Commitment to the Promotion and Development of NAMs*

FDA has repeatedly and publicly indicated its commitment to the use, promotion, and development of non-animal methodologies for years. As far back as 2010, FDA stated its intention “to issue a draft guidance to industry and to FDA staff regarding the use of [non-animal testing methods]” and “explicitly encourag[e] sponsors” to approach the agency “early in the product development process for consultation on the suitability and acceptability of non-animal tests.”³² However, over a decade later, the agency has still not issued such a guidance.

In 2017, FDA published its Predictive Toxicology Roadmap, which stated that “[d]uring the past decade, FDA scientists ha[d] taken significant steps to upgrade their toxicology toolboxes,” but that “a comprehensive strategy [wa]s [still] needed to evaluate new methodologies and technologies for their potential to expand FDA’s toxicology predictive capabilities and to potentially reduce the use of animal testing.”³³ The following year, the agency reaffirmed this understanding, recognizing that “[m]odernizing toxicology and continually improving the ability of non-clinical tests, models, and measurements to predict product safety issues will increase the likelihood that toxicology risks will be identified earlier in product development, assuring patient safety, and mitigating the need to withdraw previously approved products.”³⁴ In 2019, the agency established the FDA Alternative Methods Working Group with a mission of furthering the goals of the 2017 roadmap.³⁵

Following these statements, the agency dedicated a section on its website to alternative methods, titled Advancing Alternative Methods.³⁶ This site offers a general platform where drug sponsors and other stakeholders can find some FDA activities and publications of relevance to the 3Rs, but it does not

²⁹ AGRIC., RURAL DEV., FOOD & DRUG ADMIN., & RELATED AGENCIES APPROPRIATIONS BILL, 2024, 118TH CONG. HOUSE REPORT 81 (2024); AGRIC., RURAL DEV., FOOD & DRUG ADMIN., & RELATED AGENCIES APPROPRIATIONS BILL, SENATE REPORT, 126-127 (2024).

³⁰ Consolidated Appropriations Act, 2023, § 3209, 136 Stat. 5821-5822 (2023).

³¹ *Id.*

³² Letter from David H. Dorsey, Acting Deputy Commissioner for Policy, Planning and Budget, Food and Drugs, to Katherine A. Meyer (May 20, 2010) (denying Citizen Petition by the Mandatory Alternatives Petition Coalition).

³³ U.S. FOOD & DRUG ADMIN., FDA’S PREDICTIVE TOXICOLOGY ROADMAP 1 (2017), <https://www.fda.gov/files/science%20&%20research/published/FDA%27s-Predictive-Toxicology-Roadmap.pdf>.

³⁴ *Modernize Toxicology to Enhance Product Safety: Strategic Plan for Regulatory Science*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/science-research/advancing-regulatory-science/section-1-modernize-toxicology-enhance-product-safety-strategic-plan-regulatory-science> (last updated Mar. 29, 2018).

³⁵ *Implementing Alternative Methods*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/science-research/advancing-alternative-methods-fda/implementing-alternative-methods> (last updated Nov. 14, 2023).

³⁶ *Advancing Alternative Methods at FDA*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda> (last updated Nov. 14, 2023).

provide specific information regarding the agency’s acceptance of particular NAMs or their contexts of use.³⁷ The website describes a webinar series that invites developers to “showcase their cutting edge technologies,” but this is not open to the public so it is not possible to know whether this is widely used, whether it forms a useful platform through which the regulated community can understand potential applications of these novel technologies, or if the agency offers advice on the suitability of specific methods to the regulated community.

The most recent report on Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science, published in 2022, includes updates on some of the non-animal methods and tools that are under development in FDA labs, or form part of FDA’s research collaborations, including a human intestine on a chip model, looking for sensitive biomarkers for the adverse effects of drugs, and designing new alternative developmental neurotoxicity tests.³⁸ Over the past 15 years, FDA has also been actively engaged in applying computational modeling for regulatory testing and the development and application of artificial intelligence (“AI”) for regulatory decision making, which is an integral part of ongoing research focus at FDA’s National Center for Toxicological Research (“NCTR”). Tox-GAN is an AI-based generative adversarial network framework that employs existing animal data to generate results without additional animal testing.³⁹ It is not clear whether the Tox-GAN (or the related Animal-GAN⁴⁰) tools are fully qualified for regulatory decision making, or if data are being submitted that were generated through these platforms. Additionally, FDA was an early investor in the organ-chip or microphysiological system platforms, and the 2022 Focus Areas of Regulatory Sciences (“FARS”) report indicates that this is ongoing.⁴¹

As well as its encouragement of drug sponsors to discuss their use of innovative non-animal tools through the Advancing Alternative Methods Working group webinars, FDA also incentivizes NAMs qualification, and potentially implementation, using platforms such as the Drug Development Tools (“DDT”) Qualification tool and the Innovative Science and Technology Approaches for New Drugs (“ISTAND”) program.⁴² However, IStand is a pilot which seems to have had limited uptake, including since passage of the FDORA, since there are only two letters of intent accepted thus far and no fully qualified methods.

The latest update of the guidance document entitled Nonclinical Evaluation of the Immunotoxic Potential of Pharmaceuticals, released in June 2023, contains progressive language about the agency’s acceptance

³⁷ Petitioners note that, in contrast, the Center for Radiological Devices and Health (“CDRH”) has compiled a “Regulatory Science Tools catalog” which includes specific descriptions of in vitro and computational tools, including non-animal methods using induced pluripotent stem cell-derived cardiomyocytes to evaluate contractile responses, methods designed to assess extractable leaching in devices and to carry out fatigue loading of fixation devices. *Regulatory Science Tools Catalog*, U.S. FOOD & DRUG ADMIN., <https://cdrh-rst.fda.gov/>.

³⁸ U.S. FOOD & DRUG ADMIN., ADVANCING REGULATORY SCIENCE AT FDA: FOCUS AREAS OF REGULATORY SCIENCE (FARS) (2022), <https://www.fda.gov/media/161381/download>.

³⁹ Barbara L.F. Kaplan et al., *Protecting Human and Animal Health: The Road from Animal Models to New Approach Methods*, 76 PHARMACOLOGICAL REV. 251 (2024).

⁴⁰ *AnimalGAN Initiative*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/about-fda/nctr-research-focus-areas/animalgan-initiative> (last updated Nov. 8, 2023).

⁴¹ U.S. FOOD & DRUG ADMIN., ADVANCING REGULATORY SCIENCE AT FDA: FOCUS AREAS OF REGULATORY SCIENCE (FARS) (2022), <https://www.fda.gov/media/161381/download>.

⁴² *Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program> (last updated Mar. 15, 2024).

of NAMs. The guidance states the agency “will consider a battery of studies (e.g., in silico, in chemico, in vitro) that have been shown to adequately predict human skin sensitization with an accuracy similar to existing in vivo methods.”⁴³ Notably, however, the guidance only says the agency will “*consider*” reliance on alternative methods, while recognizing it “*accepts*” data from the guinea pig sensitization test, seeming to suggest a continued preference for the use of animal data.⁴⁴

Most recently, in its Fiscal Year 2025 budget justification, FDA stated that alternative, non-animal methodologies “have the potential to reduce animal use and provide faster and more human-relevant data than that generated by whole animal-based methods.”⁴⁵ FDA went on to state that “[n]ovel non-animal and human-specific technologies, like organ-on-a-chip technology for disease modelling, are a priority for research organizations across government, academia, and industry.”⁴⁶

3. Reasons to Grant the Requested Action

a. *FDA Regulations and Guidance Documents Misleadingly Suggest that Animal Data May Be Required for the Approval and Regulation of Drugs*

Current FDA regulations can reasonably be read to suggest that animal testing is required for the development and regulation of drugs, or at least strongly preferred by the agency when considering applications from sponsors. When in doubt if animal tests are required, drug developers are likely to conduct the traditional animal tests over selecting a non-animal method, in order to avoid having their application denied, or being forced to spend additional time and money on conducting those animal tests at a later date. This structure incentivizes drug developers to conduct tests that are time-consuming, expensive, poor predictors of safety and efficacy in humans, and ultimately not required by law, slowing the development of new therapies and unnecessarily subjecting animals to invasive, usually fatal, laboratory tests.

Despite FDA’s accurate recognition that non-animal approaches have always been an option to assess drugs under the FDCA,⁴⁷ many of the agency’s regulations as currently written seem to require, or at least express a preference for, the use of animal studies. For example, one FDA regulation requires that an IND application include “[a]dequate information about pharmacological and toxicological studies of the drug *involving laboratory animals*” and goes on to state that the “kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations.”⁴⁸ Drug developers may read this provision to suggest that while the “kind, duration, and scope” of animal tests may vary, the underlying requirement to conduct animal tests does not. Even if this reading does not reflect the true meaning of the regulation or FDA’s current thinking on the matter, the regulation’s text nevertheless provides an incentive for drug developers to conduct animal tests *just in case*, in order to ensure the advancement of their therapies and protect their profit margins. Various other FDA

⁴³ U.S. FOOD & DRUG ADMIN., NONCLINICAL EVALUATION OF THE IMMUNOTOXIC POTENTIAL OF PHARMACEUTICALS GUIDANCE FOR INDUSTRY (2023) (emphasis added).

⁴⁴ *Id.* at 3, 7.

⁴⁵ U.S. FOOD & DRUG ADMIN., CONGRESSIONAL JUSTIFICATION FISCAL YEAR 2025 153 (2024).

⁴⁶ *Id.* at 154.

⁴⁷ Donna L. Mendrick, *Advancing New Alternative Methods at FDA*, U.S. FOOD & DRUG ADMIN. (June 27, 2023), <https://www.fda.gov/media/170186/download> (“FDORA . . . [d]idn’t [c]hange the state of the science supporting the regulatory use of NAMs [and] [d]idn’t remove a ‘requirement’ for animal safety studies [because] [t]here was no such requirement to remove.”).

⁴⁸ 21 C.F.R. § 312.23(a)(8) (emphasis added).

regulations include similarly suggestive language: stating that submissions “should be supported by . . . the results of animal toxicology studies,”⁴⁹ must include summaries “of the pharmacological and toxicological effects of the drug in animals,”⁵⁰ be supported by “nonclinical studies (including animal studies),”⁵¹ and be based on a meeting “to review and reach agreement on the design of animal studies needed to initiate human testing.”⁵² See generally *supra* Section A(1) (outlining proposed changes to FDA regulations that, as currently written, may be read to suggest that animal tests are required for the approval of new drugs).

FDA regulations further point sponsors toward the agency’s guidance documents for direction on how to meet the agency’s requirements.⁵³ But many of FDA’s guidance documents suffer from the same flaw, suggesting that animal tests are required, or at least provide a greater chance of success, for the agency’s approval of drugs. In fact, this problem is even more pronounced in some of these guidance documents than it is in the relevant regulations, because many guidance documents specify particular animal tests that should be conducted and included in these applications.⁵⁴ These guidance documents do not include, on the other hand, specifics regarding NAMs that are acceptable in lieu of animal tests. While some guidance documents include a general disclaimer that the agency supports the principles of the 3Rs and may consider data from alternative methods, this generic statement cannot overcome the impression that the inclusion of specific guidelines for animal tests provides: that the agency prefers and is more likely to approve applications based on data from animal tests.

On its Advancing Alternative Methods webpages, FDA lists six guidance documents that refer to the use of alternatives for pharmaceutical testing.⁵⁵ This may be a useful introduction to the topic, but it requires that drug sponsors read all the documents to understand where non-animal tools may be applied, and it is by no means an exhaustive list. Sponsors are also encouraged to use FDA’s guidance document database, where a search for the term “in vitro” returns 67 documents. It would be time consuming, and likely off-putting, for sponsors to examine all of these to understand the relevance to a specific product

⁴⁹ 21 C.F.R. § 312.22(c).

⁵⁰ *Id.* § 312.23(a)(5)(ii).

⁵¹ *Id.* § 312.33(b)(6).

⁵² *Id.* § 312.82(a).

⁵³ *Id.* § 312.23(a)(8) (“Guidance documents are available from FDA that describe ways in which these requirements may be met.”).

⁵⁴ See, e.g., U.S. FOOD & DRUG ADMIN., ONCOLOGY THERAPEUTIC RADIOPHARMACEUTICALS: NONCLINICAL STUDIES AND LABELING RECOMMENDATIONS GUIDANCE FOR INDUSTRY (2019) (“The sponsor should conduct a biodistribution and dosimetry study in animals (typically a single dose administration) to guide dose selection . . . Both male and female animals should be included in the study . . . Biodistribution and dosimetry in large animals (e.g., monkeys) are usually done with imaging techniques; hence, a small number of animals (e.g., three males and three females) may be sufficient . . . For small animals, such as mice and rats, there should be a sufficient number of animals per time point when a method requiring animal sacrifice is used.”); U.S. FOOD & DRUG ADMIN., INVESTIGATIONAL ENZYME REPLACEMENT THERAPY PRODUCTS: NONCLINICAL ASSESSMENT GUIDANCE FOR INDUSTRY (2019) (“Healthy animals represent the standard test system employed to conduct traditional toxicological studies.”); U.S. FOOD & DRUG ADMIN., NONCLINICAL TESTING OF ORALLY INHALED NICOTINE-CONTAINING DRUG PRODUCTS GUIDANCE FOR INDUSTRY (2020) (“In general, sponsors should conduct a carcinogenicity study that involves administering novel chemicals by the inhalation route to mice or rats for 2 years . . . at a minimum, one species should be dosed by the inhalation route, and the second species should have systemic exposure to adequately assess systemic toxicity.”).

⁵⁵ *Implementing Alternative Methods*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda> (last updated Nov. 14, 2023).

and to envisage how and where in vitro tools have been used to support submissions and then relate this approach to their product.

Moreover, FDA's guidance document search tool retrieves documents dating back to the early 1990s, regardless of whether those documents are based on the best available science today or the agency's current thinking on an issue. For example, a sponsor looking for guidance on acute toxicity could retrieve a guidance document from 1996 that describes the use of animals with no reference to NAMs or even the 3R principles. The fact that these outdated guidance documents are still retrievable and have not been either updated or removed from the site makes it difficult for sponsors to identify if they reflect the current preferred methods for drug evaluation, compounding potential confusion for drug sponsors. Indeed, research has indicated that drug sponsors are still using outdated FDA guidance over more recent ICH guidelines.⁵⁶

Given this apparent prioritization of data from animal tests and failure to acknowledge the use of NAMs throughout FDA's regulations and guidance documents, it is not surprising that drug sponsors would consider it the safer—if not mandatory—route to conduct animal tests before submitting their applications to the agency. The current regulatory scheme also stunts the development of new test methods because pharmaceutical companies are actively disincentivized from using NAMs by the language in both FDA regulations and guidance documents. Without adequate assurance that the agency will accept data from NAMs, these companies are not incentivized to invest in development or use of these test methods, which are more efficient, accurate, and overall cost-effective.

FDA has repeatedly recognized the need for clarity within its regulatory landscape and taken action to ensure such clarity for the benefit of the regulated community.⁵⁷ Petitioners request the agency now take action to address the lack of clarity surrounding this key issue. FDA's clarification of its consideration and acceptance of data from NAMs will not only expedite the development of new drugs and allow for increased flexibility among drug sponsors, but also drive forward the development of additional NAMs, including more complex non-animal methods as these advance, allowing regulatory science to keep pace with innovation.

⁵⁶ Joseph Manuppello et al., *Acute Toxicity "Six-Pack" Studies Supporting Approved New Drug Applications in the U.S., 2015-2018*, 114 REG. TOXICOLOGY & PHARMACOLOGY 104666 (2020).

⁵⁷ See, e.g., *New Drugs Regulatory Program Modernization: Improving Approval Package Documentation and Communication*, 84 Fed. Reg. 30733 (Jun. 27, 2019) ("The Agency hopes to receive public feedback on both of these efforts and on how FDA might continue supporting our stakeholders' needs related to the clarity and transparency of drug approval decisions . . . In addition to the Pilot, FDA has other efforts that also seek to provide greater clarity on FDA's application review and decision-making process."); *FDA Takes Steps to Provide Clarity on Developing New Drug Products in the Age of Individualized Medicine*, U.S. FOOD & DRUG ADMIN. (Jan. 4, 2021), <https://www.fda.gov/news-events/press-announcements/fda-takes-steps-provide-clarity-developing-new-drug-products-age-individualized-medicine> ("This guidance, which provides clarity on the early development and IND submission process, is the FDA's first step in working with those who are developing these individualized drug products."); *FDA Clarifies Types of Evidence Relevant to Determining the "Intended Use" of FDA-Regulated Products*, U.S. FOOD & DRUG ADMIN. (Sep. 22, 2020), <https://www.fda.gov/news-events/press-announcements/fda-clarifies-types-evidence-relevant-determining-intended-use-fda-regulated-products> ("[A]n important step forward in fulfilling our public health mission and our promise to provide better clarity to regulated industry and other stakeholders . . . by providing additional examples and explanation in the preamble, we will give clarity to stakeholders and enhance consistency in our regulatory approach. Such clarity and consistency are critical to ensuring that parties understand their regulatory obligations and that the FDA can exercise effective oversight responsibility. For this reason, this rulemaking is an important priority for the FDA.")

b. *The Regulated Community is Demonstrably Confused by FDA's Requirements for Drug Approvals, Both Before and After the FDORA's Passage*

While the FDCA has never included a requirement to test on animals, the regulated community has for years understood—and indeed been told—otherwise. One contract research company, in response to questions about their conduct of animal studies in April 2022, stated that “[t]he research [they] do is *legally required* in the U.S. for developing lifesaving medicines, devices and biologics.”⁵⁸ One pharmaceutical company was “explicitly told” that it must conduct a nine-month study on dogs that necessarily ended in the dogs’ death, even though this apparent requirement was not supported by any relevant statute or regulation.⁵⁹

While the FDORA has been lauded by some as a fundamental change in the legal landscape of drug regulation, FDA itself recognizes that the FDORA did not actually alter its authority to accept NAMs, but merely provided “greater clarity to stakeholders regarding the potential acceptability of these alternative sources of nonclinical safety information.”⁶⁰ Moreover, the FDORA did not alter or amend the regulations or guidance documents that are the primary source of the strong suggestion that data from animal tests *are* required. Strikingly, confusion amongst the regulated community around the requirements (or lack thereof) of data from animal models for drug approval has seemingly only grown since the FDORA’s passage.

Some pharmaceutical companies have indicated that they believe the passage of the FDORA “means that new drugs do not need to be tested on animals before human studies,”⁶¹ a sentiment echoed by larger industry groups⁶² and mainstream media outlets⁶³ alike. Still other pharmaceutical companies maintain

⁵⁸ Deanna Watson, *Inotiv Responds to Humane Society’s Undercover Investigation of Animal Testing Company*, LAFAYETTE J. & COURIER (Apr. 21, 2022, 11:39 AM), <https://www.jconline.com/story/news/local/lafayette/2022/04/21/inotiv-indiana-animal-testing-laboratory-subject-undercover-investigation/7393841001/> (emphasis added).

⁵⁹ Alex Gangitano, *Drugmaker Challenges FDA on Animal Testing*, THE HILL (June 27, 2019, 6:00 AM), <https://thehill.com/regulation/court-battles/450551-drugmaker-challenges-fda-on-animal-testing/>.

⁶⁰ *Advancing Alternative Methods at FDA*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda> (last updated Nov. 14, 2023).

⁶¹ Zara Puckrin, *Alternative Testing Methods Covered by the FDA Modernization Act 2.0*, THE REPROCELL BLOG (Mar. 6, 2023), <https://www.reprocell.com/blog/biopta/alternative-testing-methods>; see also GATC Health Corp., *GATC Health Welcomes the FDA Modernization Act 2.0, Allowing New Drug Candidates to Bypass Animal Testing Using Computer Modeling*, PR NEWSWIRE (Jan. 25, 2023, 9:55 AM), <https://www.prnewswire.com/news-releases/gatc-health-welcomes-the-fda-modernization-act-2-0--allowing-new-drug-candidates-to-bypass-animal-testing-using-computer-modeling-301730522.html> (“The new legislation allows emerging technologies . . . to be used to advance drug leads to human trials without the requirement of animal testing.”).

⁶² Veronica Salib, *The FDA Modernization Act 2.0 Allows Animal Trials Alternatives*, PHARMA NEWS INTELLIGENCE (Jan. 20, 2023), <https://pharmanewsintel.com/news/the-fda-modernization-act-2.0-allows-animal-trials-alternatives> (“The FDA Modernization Act 2.0, signed by President Biden, allows clinical trial leaders to use animal trial alternatives instead of traditional animal modeling for drug and biological development.”).

⁶³ See, e.g., Joe Hernandez, *The FDA No Longer Requires All Drugs to be Tested on Animals Before Human Trials*, NPR (Jan. 12, 2023, 6:03 AM), <https://www.npr.org/2023/01/12/1148529799/fda-animal-testing-pharmaceuticals-drug-development>; Emily Anthes, *Could the Next Blockbuster Drug be Lab-Rat Free?*, N.Y. TIMES (Mar. 7, 2023), <https://www.nytimes.com/2023/03/07/health/drug-animals-testing.html>; Emily Mullin, *The US Just Greenlit High-Tech Alternatives to Animal Testing*, WIRED (Jan. 11, 2023, 11:52 AM), <https://www.wired.com/story/the-us-just-greenlit-high-tech-alternatives-to-animal-testing/>.

that even after the passage of the FDORA, “before any potential medicine can be tested in and subsequently approved for, humans, data from animal models must be submitted to the US Federal [sic] Drug Administration . . . to demonstrate its safety and efficacy.”⁶⁴

These conflicting accounts of what is or is not (or cannot be) required by FDA in the drug approval process from the industry itself is sufficient evidence of the need for FDA to amend and update, as appropriate, both its regulations and guidance documents to clarify that animal data are not required for drug approval. The issuance of the NAMs Guidance Document will ensure that drug sponsors have the information that they need if they choose to rely on data from NAMs, consistent with both Congressional intent and FDA’s repeated commitment to the acceptance of such data, *see supra* Section B(2)(b)-(c); *infra* Section B(3)(f), as well as the best available science, *see infra* Section B(3)(c), and widespread public sentiment and support, *see infra* Section B(3)(e).

c. *This Lack of Clarity Prevents Drug Developers from Relying on Data from NAMs, Even When This is the Best Available Science*

The repeated suggestion that animal data are required for the development of and approval of drugs throughout FDA’s regulations and guidance documents prevents the pharmaceutical industry from relying on data from NAMs in their submissions to the agency, even when those data are more reliable and a better predictor of effects in humans than data from studies using animals.

There is growing evidence that animal models can be poor predictors of a drug’s impact on humans, and animal tests have not been formally validated to confirm their human relevance. Advancements in science have shown that toxicity in nonhuman animals is not a reliable indicator of toxicity in humans, and—perhaps more concerningly—an absence of toxicity in nonhuman animals is not a guarantee of safety and tolerability in humans.⁶⁵ This gap in predictive accuracy between data from tests using nonhuman animals and clinical studies with humans essentially means that toxicity testing in animals in some cases may be the equivalent of tossing a coin: a review of the results from more than two hundred animal tests revealed that only 50% of these aligned with human data.⁶⁶

In addition to the already mentioned effect on the cost of drug development, this lack of reliable predictive data has serious consequences for both regulators and the public at large. It may make it more likely that individuals involved in human clinical trials are exposed to toxic substances, decrease consumers’ confidence in the safety of products, and even lead to the dismissal of compounds that may be both safe and effective in humans because they are toxic to nonhuman species. Because so-called “negative” studies—where a compound is found to be toxic to nonhuman animals—are often not published in scientific literature or even recorded in preregistration databases, it is impossible to know

⁶⁴ *Animals Used in Research*, PFIZER, <https://www.pfizer.com/science/clinical-trials/integrity-and-transparency/animals-used-in-research> (last visited Apr. 24, 2024).

⁶⁵ See e.g., Gail A. Van Norman, *Limitations of Animals Studies for Predicting Toxicity in the Clinical Trials*, 4 JACC: BASIC TO TRANS. SCI. 845 (2019); Jarrod Bailey et al., *An Analysis of the Use of Dogs in Predicting Human Toxicology and Drug Safety*, 41 ALT. TO LAB. ANIMALS 335 (2013); Thomas Hartung, *Predicting Toxicity of Chemicals: Software Beats Animal Testing*, 17 EUR. FOOD SAFETY AUTH. e170710 (2019); Matthew Clark & Thomas Steger-Hartmann, *A Big Data Approach to the Concordance of the Toxicity of Pharmaceuticals in Animals and Humans*, 96 REG. TOXICOLOGY & PHARMACOLOGY 94 (2018).

⁶⁶ Pablo Perel et al., *Comparison of Treatment Effects Between Animal Experiments and Clinical Trials: Systematic Review*, 334 BMJ 197 (2007).

how many potentially useful, or altogether revolutionary, drugs have been abandoned due to toxicity in a species other than the intended recipient species: humans.

This loss of potentially useful drugs, though, is actually the best-case scenario for this lack of predictivity in animal models. The worst-case scenario is that drugs that appear safe in nonhuman animals may go on to cause serious harm, and even death, in people.⁶⁷ For example, the drug Vioxx (rofecoxib) was originally designed to treat pain related to osteoarthritis and was approved by FDA, based on data from animal models, in 1999. Less than five years later, Vioxx had been linked to over 38,000 cardiovascular-related deaths and myocardial infarctions in human patients and was withdrawn from the market.⁶⁸ Animal studies failed to indicate the increased risk of cardiovascular events that the drug posed. Instead, it took four years of long-term clinical studies in patients, and several complex meta-analyses of these data, to show that Vioxx was responsible for increasing risk of both heart attacks and strokes in humans.⁶⁹ This is also true for drug efficacy, where it is well established that animal models of disease fail to accurately recreate the same conditions in humans, and animals genetically engineered to show symptoms of a human affliction do not offer a predictive model for finding effective treatments.⁷⁰

Even the most conservative estimates put the rate of drug failures (i.e. drugs that appear safe and effective in animal models but are not in humans) at over nine out of ten. In fact, drugs are more likely to fail now than they were fifty years ago, despite the stellar advances in science and technology that have occurred since the 1970s, including the polymerase chain reaction, sequencing the human genome, discovery of induced pluripotent stem cells, and CRISPR-Cas 9. The National Center for Advancing Translational Sciences (“NCATS”) states that “[a]pproximately 30% of promising medications have failed in human clinical trials because they are found to be toxic despite promising preclinical studies in animal models” and “[a]bout 60% of candidate drugs fail due to lack of efficacy.”⁷¹ Overall, approximately 95% of drugs that appear safe and effective in animal testing are found to be either unsafe or ineffective in humans.⁷² For drugs intended to treat cancer, this failure rate increases to ninety-six out of every hundred treatments.⁷³ For drugs intended to treat Alzheimer’s disease, failure is basically guaranteed, with a 99.6% failure rate.⁷⁴

⁶⁷ Husain Attarwala, *TGN1412: From Discovery to Disaster*, 2 J. YOUNG PHARMACISTS 332 (2010).

⁶⁸ Peter Jüni et al., *Risk of Cardiovascular Events and Rofecoxib: Cumulative Meta-Analysis*, 364 THE LANCET 2021 (2004).

⁶⁹ Hans-Karl Heim & Karl Broich, *Selective Cox-2 Inhibitors and Risk of Thromboembolic Events – Regulatory Aspects*, 96 THROMBOSIS & HAEMOSTASIS 423 (2006).

⁷⁰ Francesca Pistollato et al., *Alzheimer Disease Research in the 21st Century: Past and Current Failures, New Perspectives and Funding Priorities*, 7 ONCOTARGET 38999 (2016); Lindsay J. Marshall & Catherine Willett, *Parkinson’s Disease Research: Adopting a More Human Perspective to Accelerate Advances*, 23 DRUG DISCOVERY TODAY 1950 (2018); Pascaline Clerc et al., *A Look into the Future of ALS Research*, 21 DRUG DISCOVERY TODAY 939 (2016).

⁷¹ *Tissue Chip Frequently Asked Questions*, NAT’L. CTR. FOR ADVANCING TRANSLATIONAL SCI., <https://ncats.nih.gov/research/research-activities/tissue-chip/faq> (last updated Apr. 22, 2024).

⁷² *New Therapeutic Uses*, NAT’L. CTR. FOR ADVANCING TRANSLATIONAL SCI., <https://ncats.nih.gov/research/research-activities/ntu> (last updated Apr. 19, 2024); Deloitte, *R & D, 2023 GLOBAL LIFE SCIENCES OUTLOOK (2023)*, <https://www2.deloitte.com/content/dam/Deloitte/ch/Documents/life-sciences-health-care/deloitte-ch-life-sciences-outlook-2023-r-d-report.pdf>.

⁷³ Chi Heem Wong et al., *Estimation of Clinical Trial Success Rates and Related Parameters*, 20 BIostatistics 273 (2019).

⁷⁴ Jeffrey L. Cummings et al., *Alzheimer’s Disease Drug-Development Pipeline: Few Candidates, Frequent Failures*, 6 ALZHEIMER’S RES. & THERAPY 37 (2014).

Researchers have referred to this translational failure inherent in animal testing as an “insurmountable problem of species difference” that, when combined with continued reliance on poorly predictive animal models, has pushed drug development into crisis.⁷⁵ Development costs are increasing,⁷⁶ clinical trial failures are reported on an almost daily basis,⁷⁷ and the number of new drug approvals is stagnating. In the last decade, on average fewer than 50 new molecular entities received FDA approval each year.⁷⁸

There are, however, alternatives to these animal models—NAMs—that do not suffer from the same translational failures. There is ever-increasing evidence that NAMs may provide superior results to traditional animal models, at least at the single organ level, and increasingly these are evolving to integrated, multi-organ systems.⁷⁹ One such multicellular, single organ non-animal NAM, the Emulate liver chip, underwent extensive testing using small molecules identified as benchmarks for hepatotoxicity by the Innovation and Quality consortium.⁸⁰ The testing included known hepatotoxicants and non-toxic molecules, where the toxicants had all been flagged as safe through nonhuman animal testing but had triggered serious adverse effects when given to the human patient population, including several fatalities. The liver chip demonstrated more than 87% specificity—accurately identifying seven out of every eight of the known toxicants as dangerous—and 100% sensitivity, indicating that the use of chips may be a more reliable method to screen out toxic drugs in the development stage. This suggests that reliance on such data over data from animal studies could prevent potentially toxic drugs from proceeding into human trials and even to market. Drug-induced liver injury (“DILI”) is the cause of the majority of post-approval drug withdrawals, but it is not flagged in animal studies.⁸¹ The implementation of these chips could not only increase human safety and prevent fatalities, but also have a massive economic impact. The increase in productivity that the liver chip offers for small molecule drug testing has been estimated at approximately \$3 billion annually.⁸² The exorbitant cost of drugs today is at least in part due to the industry’s need to factor in losses accrued by drug failures and post-approval withdrawals. Improving predictivity with more relevant tools could therefore reduce these losses, ultimately making drugs more accessible to the American public. Additionally, incorporation of liver chips into a nonclinical testing workflow at the stage of lead optimization, would reveal compounds with unacceptable toxicity profiles, halting further development, and so could help to reduce animal testing since these compounds are unlikely to prove safe for the intended (human) population.

⁷⁵ Pandora Pound & Christine J. Nicol, *Retrospective Harm Benefit Analysis of Pre-Clinical Animal Research for Six Treatment Interventions*, 13 PLOS ONE e0193758 (2018).

⁷⁶ Jack W. Scannell et al., *Diagnosing the Decline in Pharmaceutical R&D Efficiency*, 11 NATURE REV. DRUG DISCOVERY 191 (2012).

⁷⁷ Annalee Armstrong, *2023’s Top 10 Clinical Trial Flops*, FIERCE BIOTECH (Jan. 22, 2024, 6:00 AM), <https://www.fiercebiotech.com/special-reports/2023s-top-10-clinical-trial-flops>.

⁷⁸ U.S. FOOD & DRUG ADMIN., NOVEL DRUG APPROVALS AT FDA (Apr. 8, 2024), <https://www.fda.gov/drugs/development-approval-process-drugs/novel-drug-approvals-fda>.

⁷⁹ Nathalie Picollet-D’hahan et al., *Multiorgan-on-a-Chip: A Systemic Approach to Model and Decipher Inter-Organ Communication*, 39 TRENDS BIOTECHNOLOGY 788 (2021).

⁸⁰ Lorna Ewart et al., *Performance Assessment and Economic Analysis of a Human Liver-Chip for Predictive Toxicology*, 2 NATURE COMMUNICATIONS MEDICINE (154, 2022).

⁸¹ Amy M. Avila et al., *An FDA/CDER Perspective on Nonclinical Testing Strategies: Classical Toxicology Approaches and New Approach Methodologies (NAMs)*, 114 REG. TOXICOLOGY & PHARMACOLOGY 104662 (2020).

⁸² Lorna Ewart et al., *Performance Assessment and Economic Analysis of a Human Liver-Chip for Predictive Toxicology*, 2 NATURE COMMUNICATIONS MEDICINE (154, 2022).

Another example of the promise of NAMs over animal studies is the use of a three-dimensional multi-cellular liver approach applied to modeling, nonalcoholic steatohepatitis (“NASH”). NASH is reaching epidemic proportions across the globe, and its precursor, non-alcoholic fatty liver disease (“NAFLD”), impacts the lives of almost one-quarter of American adults. In efforts to address these afflictions, animal models are based on artificial pathology (either through diet modulation or genetic modifications that do not reflect human disease progression) and have consistently failed to reveal potential treatments.⁸³ Recently, human liver tissue models have been bioprinted using hepatic stellate cells, liver sinusoidal endothelial cells, and Kupffer cells.⁸⁴ Models created using patient cells developed a typical NASH phenotype, in the absence of any stimulation with disease inducing agents, demonstrating the potential utility of these fully human models in revealing drug targets and for developing and testing therapies.⁸⁵

The use of human cell and data-based approaches to modeling the rarest diseases is perhaps one of the most attractive propositions for these tools. As defined by the FDA’s Orphan Drug Act of 1983, rare diseases are conditions affecting fewer than 200,000 Americans,⁸⁶ and they are both under-researched and often poorly understood. Of the 7,000 rare diseases for which the molecular cause is known, fewer than 500 have treatments.⁸⁷ This is due in part to the lack of any useful models. For rare diseases, there are often no options to use animals, either because not enough is known about the etiology of the condition to begin to develop an animal model or because attempts to create an animal model have failed. In these cases, the use of patient-derived cells or tissues can offer a valid model system. In fact, there are demonstrable successes applying human relevant approaches for modelling rare diseases in order to develop effective therapeutics. This area could allow better understanding of how and where these new tools already offer advantages over the use of animals, ensuring that all drug sponsors are aware of, and understand how, NAMs data have been used for investigating drug safety and efficacy in rare diseases offers a strong incentive for further development and use of NAMs.

For the rare, fatal genetic condition cystic fibrosis (“CF”), which affects around 40,000 Americans, genetically modified mice, used for decades as animal models of CF, fail to develop any of the respiratory symptoms that are so damaging for human patients.⁸⁸ But epithelial organoids from patients have been used to demonstrate the efficacy of the small molecule channel modifiers that are proving to be game changing for people with CF.⁸⁹ More recently, an integrated neuromuscular junction organ chip was used to show that a previously approved drug could prevent the complement activation that led to demyelination in people with chronic inflammatory demyelinating polyneuropathy, and these data were accepted, in lieu of animal data, to move the molecule to clinical trial.⁹⁰

⁸³ Joost Boeckmans et al., *Human-Based Systems: Mechanistic Nash Modelling Just around the Corner?*, 134 PHARMACOLOGICAL RES. 257 (2018).

⁸⁴ Philip K. Tan, *Role of Hepatic Stellate and Liver Sinusoidal Endothelial Cells in a Human Primary Cell Three-Dimensional Model of Nonalcoholic Steatohepatitis*, 194 AM. J. PATHOLOGY 353 (2024).

⁸⁵ Anna Loewa et al., *Human Disease Models in Drug Development*, 1 NATURE REV. BIOENGINEERING 545 (2023).

⁸⁶ U.S. FOOD & DRUG ADMIN., RARE DISEASES AT FDA (Dec. 13, 2022), <https://www.fda.gov/patients/rare-diseases-fda>.

⁸⁷ NAT’L. INST. HEALTH, THE PROMISE OF PRECISION MEDICINE: RARE DISEASES (Nov. 16, 2023), <https://www.nih.gov/about-nih/what-we-do/nih-turning-discovery-into-health/promise-precision-medicine/rare-diseases#:~:text=Advances%20in%20diagnosis%20of%20rare,about%20500%20have%20approved%20treatments.>

⁸⁸ Lindsay J. Marshall & Kathleen M. Conlee, *The Case of the Missing Mouse—Developing Cystic Fibrosis Drugs without Using Animals*, 4 FRONTIERS IN DRUG DISCOVERY (2024).

⁸⁹ *Id.*

⁹⁰ John W. Rumsey et al., *Classical Complement Pathway Inhibition in a “Human-on-a-Chip” Model of Autoimmune Demyelinating Neuropathies*, 5 ADVANCED THERAPEUTICS 197 (2022).

FDA is, of course, well-aware of the benefits of NAMs, and it has played a key role in the development and initial acceptance of data from NAMs. The comprehensive in vitro pro-arrhythmia assay (“CiPA”) is a non-animal, human-relevant approach that was developed with extensive input from FDA and has since been incorporated into international guidance documents.⁹¹ In 2019, FDA demonstrated utility of this tool to detect drug-induced pro-arrhythmic effects.⁹² In 2020, FDA scientists published a sensitivity analysis of calibration drugs for classification thresholds, using CiPA as the standard.⁹³ CiPA offers a compelling example of where non-animal tools can be developed to fulfil a regulatory need. FDA has also recognized the potential of NAMs to replace the limulus amoebocyte lysate assay, or the use of live rabbits for assessing pyrogens. The FDA guidance document on pyrogen and endotoxins testing states that “a firm may substitute an endotoxins test or alternative cell-based test if the firm can demonstrate equivalent pyrogen detection.”⁹⁴ Finally, FDA was an early supporter of the microphysiological systems technologies, entering into a Memorandum of Understanding with the NCATS to “promote the advancement of Microphysiological Systems.”⁹⁵ This collaboration has led to the establishment of Translational Centers, institutions that will be responsible for the development of microphysiological systems that can be applied in the development of drugs for liver and kidney disease, as well as central nervous system and other so-called “barrier” disorders.⁹⁶ Notably, the ultimate aim of the Translational Centers is to submit full qualification packages to FDA that will enable validation of these methods as fully non-animal tools for drug development.⁹⁷

Despite these significant steps toward the development and implementation of NAMs, the current state of FDA’s regulations and many guidance documents suggest that animal data is sometimes nevertheless required for FDA approval, even when there are NAMs available with demonstrably better outcomes for long-term drug development, efficacy, and safety. Making the changes to FDA regulations and guidance documents recommended herein would thus better serve the regulated community and promote the development of new drugs and therapies for American consumers.

⁹¹ See David Strauss et al., *Translational Models and Tools to Reduce Clinical Trials and Improve Regulatory Decision Making for QTc and Proarrhythmia Risk (ICH E14/S7B Updates)*, 109 CLINICAL TOXICOLOGY & THERAPEUTICS 319 (2021); U.S. FOOD & DRUG ADMIN., E14 AND S7B CLINICAL AND NONCLINICAL EVALUATION OF QT/QTc INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL—QUESTIONS AND ANSWERS GUIDANCE FOR INDUSTRY (2022).

⁹² David Strauss et al., *Comprehensive in Vitro Proarrhythmia Assay (CiPA) Update from a Cardiac Safety Research Consortium / Health and Environmental Sciences Institute / FDA Meeting*, 53 THERAPEUTIC INNOVATION & REG. SCI. 519 (2019).

⁹³ Zhihua Li et al., *General Principles for the Validation of Proarrhythmia Risk Prediction Models: An Extension of the CiPA in Silico Strategy*, 107 CLINICAL PHARMACOLOGY & THERAPEUTICS 102 (2020).

⁹⁴ U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY PYROGEN AND ENDOTOXINS TESTING: QUESTIONS AND ANSWERS (2012).

⁹⁵ U.S. FOOD & DRUG ADMIN., MOU 225-23-003: MEMORANDUM OF UNDERSTANDING BETWEEN THE NATIONAL INSTITUTES OF HEALTH (NCATS) AND THE FOOD AND DRUG ADMINISTRATION (FDA) FOR THE MICROPHYSIOLOGICAL SYSTEMS PROGRAM (2023).

⁹⁶ *Grants Guide*, DEP’T. OF HEALTH & HUMAN SERV., <https://grants.nih.gov/grants/guide/rfa-files/RFA-TR-23-001.html#:~:text=The%20National%20Center%20for%20Advancing,use%20of%20MPS%20for%20disease> (last visited Apr. 25, 2024).

⁹⁷ Amy M. Avila et al., *An FDA/CDER Perspective on Nonclinical Testing Strategies: Classical Toxicology Approaches and New Approach Methodologies (NAMs)*, 114 REG. TOXICOLOGY & PHARMACOLOGY 104662 (2020) (noting CDER has examined the readiness of NAMs to replace animal data in regulatory decision-making, while also identifying problems with reliance on animal data, stating that while it is receptive to NAMs “a relatively standard set of studies has evolved” in the process of drug development, the majority of which rely on nonhuman animal studies. This analysis acknowledges that there are critical areas of risk where animal data underperform, such as drug induced liver injury).

d. *This Lack of Clarity is Likely to Lead to Increased Confusion and Challenges to FDA’s Regulatory Scheme*

This lack of clarity in agency regulation may have negative unintended consequences for not only the regulated community and the American public, as outlined above, but also for the regulatory agency. Unclear or inconsistent regulations are likely to lead to legal challenges and other disputes, tying both those subject to the regulations and the promulgating agency up in court for years. This is, of course, an avoidable waste of agency resources, and it also has the potential to further hinder the development of new drugs by the regulated community while they wait for resolution through the legal system.

This dilemma is increasingly likely given both recent Supreme Court precedent and a growing commitment to non-animal test methods. FDA has already faced lawsuits challenging its regulation of drugs and the use of animal tests.⁹⁸ Such claims are likely to increase as both the availability of and the public’s support for non-animal test methods continue to grow. Litigation takes a significant toll on agency (and drug sponsor) resources, preventing all actors from focusing on progress in other areas, but it also risks further muddying the regulatory pathway if courts in different jurisdictions reach different conclusions.

When courts are called on to evaluate regulations that are unclear, the Supreme Court has instructed them to “sometimes” defer to the authoring agency’s interpretation and “sometimes not.”⁹⁹ Such deference is to be given only after a court concludes “that a rule is genuinely ambiguous” by “exhaust[ing] all the ‘traditional tools’ of construction.”¹⁰⁰ In other words, an agency’s interpretation of its own regulation may receive deference, but it is much more likely not to, following the Supreme Court’s cabining of the so-called Auer deference doctrine in 2019. This leads to a scheme where more individual district courts across the country will be called on to decide what a regulation means, rather than quickly “wav[ing] the ambiguity flag” and deferring to the agency’s interpretation.¹⁰¹ If courts reach different conclusions as to what a regulation means, the regulated community may not know which interpretation to comply with, or may default to taking no action while the differing interpretations are challenged up through the Courts of Appeals. This scheme could only act as a disincentive for drug sponsors to develop new drugs. Drug sponsors may be stuck in a state of limbo where their choices are to not act at all—massively delaying or even halting the development of direly needed medications—or to try to comply with all interpretations. This only compounds the harm inherent in unclear or inconsistent regulations: drug sponsors are more likely to spend more time and money on more unnecessary tests in an attempt to comply with multiple, conflicting sources of authority; delaying development (and therefore approval) of new drugs, harming the American public; all while creating a more difficult scheme for FDA to administer and communicate to the regulated community.

⁹⁸ See, e.g., *Vanda Pharms., Inc. v. Food & Drug Admin.*, 436 F. Supp. 3d 256 (D.D.C. 2020) (challenging FDA’s clinical hold on an experimental drug until sponsor conducted a toxicity study on non-rodent animals).

⁹⁹ *Kisor v. Wilkie*, 588 U.S. 558, 563 (2019).

¹⁰⁰ *Id.* at 575.

¹⁰¹ *Id.*

e. *The Requested Action Would Align with Public Support for the Acceptance and Development of Non-Animal Test Methods*

Of course, the lack of clarity in FDA’s regulations and guidance documents regarding the necessity of animal test data also negatively impacts animals. As long as there is a lack of clear guidance as to the acceptance of NAMs, it is understandable that drug sponsors are likely to resort to the path of least resistance and rely on traditional animal methods. This is particularly true for smaller and less experienced sponsors, who rely on contract research organizations for preclinical testing data. But anytime an animal study is conducted unnecessarily—i.e. when an appropriate non-animal alternative is available—animals are being needlessly killed. FDA could prevent this unnecessary use of animals by providing industry with clear information about its acceptance of NAMs.

Moreover, activities that accelerate the replacement of animals in testing are widely supported by the American public. A 2018 opinion poll of US adults from the Pew Research Center indicated that the majority of the public are in opposition to the use of animals for scientific research, and these data reflect longstanding views.¹⁰² National polls commissioned by the Foundation for Biomedical Research have indicated a steady decline in support for animal testing, from 62% in 2004, to 54% in 2008, and falling to a minority of 48% in 2016.¹⁰³ These data are consistent with Gallup’s Values and Beliefs polls that have observed a decline in the number of Americans who support animal testing and revealed that over two-thirds of Americans are “concerned” about the use of animals in experiments.¹⁰⁴ The most recent Gallup poll of US adults indicates a significant shift in thinking, with more people now believing that animal research is morally wrong, and the belief that animal research for medical purposes is morally acceptable is at an all-time low.¹⁰⁵ A poll of 1500 Americans conducted in April 2022 found that 71% think the government should invest in developing non-animal methods that could reduce or eliminate the use of animals.¹⁰⁶

f. *The Requested Action Would Align With FDA’s Commitment to the Acceptance and Development of NAMs*

Making the changes requested herein would also help to fulfill the agency’s prior commitments to the use and advancement of NAMs. The agency has recognized that promoting the use of—and development of additional—NAMs will better serve both the regulated community and the nation as a whole, which depends on the timely and safe approval of new drugs and treatments. While the agency has maintained

¹⁰² Cary Funk & Meg Hefferon, *Most Americans Accept Genetic Engineering of Animals That Benefits Human Health, but Many Oppose Other Uses*, PEW RES. CTR. (Aug. 16, 2018), <https://www.pewresearch.org/science/2018/08/16/most-americans-accept-genetic-engineering-of-animals-that-benefits-human-health-but-many-oppose-other-uses/>.

¹⁰³ David Q. Beversdorf & Nellie R. Adams, *Attitudes Toward Animal Research Among Medical Students in the United States*, 59 J. AM. ASS’N. LAB. ANIMAL SCI. 120 (2020).

¹⁰⁴ *Moral Issues*, GALLUP, <https://news.gallup.com/poll/1681/moral-issues.aspx> (last visited Apr. 25, 2024).

¹⁰⁵ *Id.*

¹⁰⁶ Kitty Block & Sara Amundson, *California Senate Committee Advances Bill to Prohibit Certain Toxicity Tests on Dogs*, THE HUMANE SOCIETY OF THE U.S.: A HUMANE WORLD BLOG (Apr. 7, 2021), <https://www.humane-society.org/blog/california-senate-committee-advances-bill-prohibit-certain-toxicity-tests-dogs-hsus-poll-shows> (discussing Remington Research Group poll).

a public commitment to NAMs,¹⁰⁷ the fact remains that for the regulated community, the most reliable source of information regarding the data the agency will or will not accept is the agency's regulations and specific guidance documents. Because drug developers are understandably concerned with minimizing risk and expediting approval, they are likely to default to complying with the strictest interpretations of regulations and guidance documents because those materials carry more legal weight than generalized agency statements. As such, no matter what statements FDA makes publicly, it will not be able to fully realize these commitments unless and until it changes its regulations and public-facing guidance documents to ensure that drug developers understand both that NAMs are accepted for new drug applications and which NAMs the agency accepts in lieu of costly and inefficient animal tests. The changes requested in this petition will not require the use of one test method over another, but rather are intended to make clear to the regulated community the complete range of types of data accepted by the agency for the purposes of approving the use and marketing of drugs. When to utilize NAMs—or traditional animal testing methods—will remain completely within the agency and the drug developer's discretion. Making clear to the regulated community that it has the *option* to use scientifically recognized modern test methods in lieu of traditional animal tests will allow for increased flexibility for the regulated community, promoting the efficient and effective development and approval of drugs and therapies.

4. Conclusion

For all the foregoing reasons, Petitioners respectfully request that the Commissioner take action to revise existing regulations that suggest animal testing is required where it is not, issue a new guidance document detailing NAMs accepted by FDA, and include language regarding FDA's acceptance of NAMs in all current and future relevant guidance documents. These actions will provide clarity to the regulated community; promote the safe, efficient, and cost-effective development of drugs in the United States; and further FDA's commitment to the development and use of non-animal test methods.

Petitioners stand ready to assist or provide any additional information that may be needed to grant this Petition. All information relied upon herein is attached in full in accordance with 21 C.F.R. § 10.20(c). Letters from over 160,000 individuals signaling support for the acceptance of non-animal test methods are also attached.

C. ENVIRONMENTAL IMPACT

The actions Petitioners request herein qualify for a categorical exclusion from the environmental assessment requirement under 21 C.F.R. § 25.30(h).

D. ECONOMIC IMPACT

Petitioners will submit an economic impact evaluation of the action requested herein if requested by the Commissioner following review of the petition, in accordance with 21 C.F.R. § 10.30(b)(3).

¹⁰⁷ See, e.g., David Strauss, *FDA/CDER FDA Update on Advancing Alternatives for Regulatory Use*, U.S. FOOD & DRUG ADMIN., (May 26, 2022), https://ntp.niehs.nih.gov/sites/default/files/iccvam/meetings/iccvam-forum-2022/present/07_strauss_508.pdf.



E. CERTIFICATION

As required by 21 C.F.R. § 10.30(b)(3), the undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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