CRS
CENTER FOR RESPONSIBLE SCIENCE

animal wellness action

CENTER FOR A HUMANE ECONOMY

animal wellness foundation

VIA US mail and Email

August 28, 2023

Robert M. Califf, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Califf:

On behalf of Animal Wellness Action (AWA), the Center for a Humane Economy (CHE), and the Center for Responsible Science (CRS), we are writing to initiate a discussion regarding the need for regulatory updates regarding product development overseen by your agency.

In 2015, CRS and 17 co-petitioners filed a Citizens Petition under Sections 505, 515 and 701 of the Federal Food, Drug, and Cosmetic Act ("FDCA" or "the Act") 21 U.S.C. §§ 355, 360, 360e, 371, and Section 351 of the Public Health Service Act ("PHS Act") 42 U.S.C. § 262 (Docket FDA-2015-P-2820, Citizens Petition) requesting FDA modify existing regulations in Title 21 of the Code of Federal Regulations (CFR) that govern requirements for investigational new drug (IND) applications, investigational device exemptions (IDE), and new drug applications (NDAs). The petition specifically requested a revised definition of "preclinical or nonclinical" that was test-neutral, and to update regulations that facially require the use of animals to test-neutral language. Your agency provided two interim responses, but a substantive response was never issued.

In 2021, AWA and CHE spearheaded the legislative effort, now known as the FDA Modernization Act 2.0 (FDAMA). On December 29, 2022, President Joe Biden signed the FDAMA into law as part of the Omnibus Appropriations Bill for FY 2023. The FDAMA had garnered a strong bipartisan support in the 117th U.S. Congress and was welcomed by the FDA. It also received considerable backing from industry, academia, non-profit organizations, and animal welfare groups.

Among the simple but consequential changes of the FDAMA is a specific amendment to the Federal Food, Drug, and Cosmetic Act (FDCA) replacing the term "preclinical tests (including tests on animals)" with "nonclinical tests" in Section 505 of the Act (21 U.S.C. 355).

In practical terms, the legislation revised the long-standing statute on the use of animal models to support new drug applications, urging - when applicable - the use of non-animal alternatives, also known as New Approach Methodologies, to predict the safety and effectiveness of a drug in nonclinical testing stages. As defined, nonclinical tests include tests conducted "*in vitro, in silico, or in chemico*" methods. Similarly, "*non-animal or human biology-based test methods include cell-based assays, microphysiological systems, or bioprinted or computer models.*"

Agency regulations are promulgated in accordance and conformity with Congress's statutory language and intent; therefore, if a rule conflicts with a statute, the statute will prevail, and the rule will be set as void to the extent it conflicts with the enabling statute. As the amended FDCA now stands, FDA's current regulations related to animal testing are no longer compliant with the statutory language. **Therefore, we ask that the FDA initiate notice and commence rulemaking to modify existing regulations to conform with the amended FDCA.**

For your convenience, we provide in Exhibits A and B a non-exhaustive list where changes are needed. For example, the following sections of 21 C.F.R need to be updated to reflect test-neutral language: §§3.7, 10.20, 14.95, 16.1, 50.24, 58.3, 201.56, 201.57, 201.80, 201.1, 312.32, 312.160, 314.81, 314.200, 314.430, 316.20, 330.14, 343.80, 361.1.

We welcome the opportunity to meet with you at your earliest convenience to discuss this matter and to assist in making the necessary changes as soon as possible.

Sincerely,

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Gerry R. Boss, MD
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The following two paragraphs provide additional information concerning the CRS Citizens Petition.

The petition requests specific language updates for 312.22, 312.23, 312.33, 312.82, 312.88, 312.160, 314.50, 314.93, 315.6, 330.10, 601.35, 812.2, 812.5, 812.27, 812.35, 860.5, 860.7. Additionally, the petition requested that an updated definition of "preclinical" or "nonclinical" testing, studies or tests with test-neutral language be issued and placed under definition sections of 21 C.F.R. §§ 3.7, 58.3, 310.3, 312.3, 314.3, 315.2, 601.31, 812.3, 860.3. In light of the updated statute, the definition needs to conform with the statute. (Current and proposed language in Exhibit A below).

To provide regulatory consistency, the following additional sections of 21 C.F.R need to be updated to reflect test-neutral language: §§3.7, 10.20, 14.95, 16.1, 50.24, 58.3, 201.56, 201.57, 201.80, 201.1, 312.32, 312.160, 314.81, 314.200, 314.430, 316.20, 330.14, 343.80, 361.1. (See attached Exhibit B).

Exhibit A Regulation Updates

To conform with the updates to the Federal Food Drug and Cosmetics Act, the following regulatory text must be issued and placed under the definition sections of 21 C.F.R. §§ 310.3, 312.3, 314.3, 315.2, 601.31, 812.3, 860.3:

Nonclinical test defined
"Nonclinical test" means 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 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.

1. 21 C.F.R. § 312.22(c) (General Principles for IND Submissions)

Proposed: *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 ~~animal~~ nonclinical toxicology studies or other human studies as appropriate. . . .*

2. 21 C.F.R. § 312.23(a)(3)(iv) ((IND Content and Format)

Proposed: *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 ~~in animals~~ from nonclinical or prior studies in humans with the drug or related drugs.*

3. 21 C.F.R. § 312.23(a)(5)(ii) (IND Investigator's Brochure)

Proposed: *A summary of the pharmacological and toxicological effects of the drug in ~~animals~~ nonclinical tests and, to the extent known, in humans.*

4. 21 C.F.R. § 312.23(a)(5)(iii) (Investigator's Brochure)

Proposed: *A summary of the pharmacokinetics and biological disposition of the drug in ~~animals~~ nonclinical tests and, if known, in humans.*

5. 21 C.F.R. § 312.23(a)(8) (IND Pharmacology and Toxicology Information)

Proposed: *Pharmacology and toxicology information. Adequate information about pharmacological and toxicological studies of the drug involving ~~laboratory animals or in vitro~~ nonclinical tests, 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 ~~animal and other tests~~ nonclinical tests required varies with the duration and nature of the proposed clinical investigations. . . .

6. 21 C.F.R. § 312.23(a)(8)(i) (Pharmacology and Drug Disposition)

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

7. 21 C.F.R. § 312.23(a)(8)(ii) (Toxicology)

Proposed: *Toxicology. (a) An integrated summary of the toxicological effects of the drug in ~~animals and in vitro~~ nonclinical tests. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; ~~preclinical~~ 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); and any in vitro studies intended to evaluate drug toxicity.*

8. 21 C.F.R. § 312.23(a)(10)(i) (Drug Dependence and Abuse Potential)

Proposed: *Drug dependence and abuse potential. If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in ~~test animals~~ nonclinical tests.*

9. 21 C.F.R. § 312.23(a)(10)(ii) (Radioactive Drugs)

Proposed: *Radioactive drugs. If the drug is a radioactive drug, sufficient data from ~~animal~~ nonclinical 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. . . .*

10. 21 C.F.R. § 312.33(a)(6) (Content of Annual Reports)

Proposed: *A list of the ~~preclinical~~ nonclinical studies ~~(including animal studies)~~ completed or in progress during the past year and a summary of the major ~~preclinical~~ nonclinical findings.*

11. 21 C.F.R. § 312.82(a) (Early Consultation)

Proposed: *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 ~~animal~~ nonclinical studies needed to initiate human testing. . . .*

12. 21 C.F.R. § 312.88 (Safeguards for Patient Safety)

Proposed: *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 ~~animal~~ nonclinical studies prior to initial human testing (¤ 312.23) . . . .*

13. 21 C.F.R. § 312.160 (Drugs for Investigational Use in ~~Laboratory Research Animals on In Vitro Tests~~ in Nonclinical Tests).

Proposed: *Drugs for investigational use in ~~laboratory research animals or in vitro~~ nonclinical tests. . . . A person may ship a drug intended solely for ~~tests in vitro or in animals used only for laboratory research purposes~~ nonclinical tests if it is labeled as follows:*
CAUTION: Contains a new drug for investigational use only in ~~laboratory research animals or for tests in vitro~~ nonclinical tests.. Not for use in humans. . . . (2) A person shipping a drug under paragraph (a) of this section shall use due diligence to assure that the consignee is regularly engaged in conducting such tests and that the shipment of the new drug will actually be used for nonclinical testing ~~tests in vitro or in animals used only for laboratory research.~~

14. 21 C.F.R. § 314.50(d)(2) (NDA Technical Sections)

Proposed: *Nonclinical pharmacology and toxicology section. A section describing, with the aid of graphs and tables, ~~animal and in vitro~~ nonclinical studies with drug . . . .*

15. 21 C.F.R. § 314.50(d)(2)(iv) (NDA Non-Clinical Sections)

Proposed: *Any nonclinical studies of the absorption, distribution, metabolism, and excretion of the drug ~~in animals~~.*

16. 21 C.F.R. § 314.50(d)(5)(i) (Clinical Data Section)

Proposed: *A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the ~~animal~~ nonclinical pharmacology and toxicology data.*

17. 21 C.F.R. § 314.50(d)(5)(vi)(a) (Clinical Data Section)

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

18. 21 C.F.R. § 314.50(d)(5)(vi)(b) (Clinical Data Section)

Proposed: *(b) The applicant shall, 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, ~~animal studies~~ nonclinical studies, and other sources) and are required to be submitted in the same format . . . .*

19. 21 C.F.R. § 314.93(e)(2) (ANDA Petition to Request Change from Listed Drug)

Proposed: *For purposes of this paragraph, "investigations must be conducted" means that information derived from ~~animal~~ nonclinical or clinical studies is necessary to show that the drug product is safe or effective. Such information may be contained in published or unpublished reports.*

20. 21 C.F.R. § 315.6(d) (Evaluation of Safety)

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

21. 21 C.F.R. § 330.10 (a)(2) (Procedure for Establishing OTC Drug Monographs)

Proposed: *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. ~~Animal~~ Nonclinical safety data . . . .

22. 21 C.F.R. § 601.35(d) (Diagnostic Radiopharmaceuticals)

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

23. 21 C.F.R. § 812.2(c) (IDE Exempted Investigations)

Proposed: *Exempted investigations. This part, with the exception of § 812.119, does not apply to investigations of the following categories of devices . . . . (6) A device shipped solely for nonclinical research ~~on or with laboratory animals~~ and labeled in accordance with § 812.5(c).*

24. 21 C.F.R. § 812.5(c) (Labeling of Investigational Devices)

Proposed: *~~Animal~~ Nonclinical research. An investigational device shipped solely for nonclinical research ~~on or with laboratory animals~~ shall bear on its label the following statement: "CAUTION--Device for investigational use in ~~laboratory animals~~ nonclinical or other tests that do not involve human subjects."*

25. 21 C.F.R. § 812.27(a) (IDE Report on Prior Investigations)

Proposed: *General. The report of prior investigations shall include reports of all prior clinical~~, animal,~~ and nonclinical ~~laboratory~~ testing of the device and shall be comprehensive and adequate to justify the proposed investigation.*

26. 21 C.F.R. § 812.35(a)(3)(iii) (Supplemental Applications)

Proposed: *Definition of credible information. (A) Credible information to support developmental changes in the device (including manufacturing changes) includes data generated under the design control procedures of § 820.30, ~~preclinical/animal~~ nonclinical testing, peer reviewed published literature, or other reliable information such as clinical information gathered during a trial or marketing.*

27. 21 C.F.R. § 860.5(f) (Medical Device Classification Procedures)

Proposed: *For purposes of this section, safety and effectiveness data include data and results derived from all nonclinical studies and tests of a device, studies and tests of a device on ~~animals and~~ humans, and from all studies and tests of the device itself intended to establish or determine its safety and effectiveness.*

28. 21 C.F.R. § 860.7(d)(2) (Determination of Safety and Effectiveness)

Proposed: *Among the types of evidence that may be required, when appropriate, to determine that there is reasonable assurance that a device is safe are investigations using ~~laboratory animal~~ nonclinical studies and investigations involving human subjects.~~, and nonclinical investigations including in vitro studies.~~*

Exhibit B

In addition, the following regulations must be updated:
To provide regulatory consistency, the following additional sections of 21 C.F.R must be updated to reflect test-neutral language: §§3.7, 10.20, 14.95, 16.1, 50.24, 58.3, 201.56, 201.57, 201.80[1], 201.1, 312.32, 312.160, 314.81, 314.200, 314.430, 316.20, 330.14, 343.80, 361.1.

Specific test---neutral language:

Section	**Current language**	**Proposed test---neutral language**
§3.7	Animal or clinical studies	Preclinical/nonclinical or clinical studies
§10.20	Animals and humans	Preclinical/nonclinical and humans
§14.95	Animal studies	Preclinical/nonclinical studies
§16.1	animals and humans	Preclinical/nonclinical and humans
§50.24	animal and other preclinical studies	Preclinical/nonclinical studies
§58.3	In vivo or in vitro experiments	Animal and non---animal experiments
§201.56	Animal data Animal Toxicology Animal toxicity	Preclinical/nonclinical data Preclinical/nonclinical Toxicology Preclinical/nonclinical toxicity
§201.57	Human, animal, and/or pharmacologic Animal data Animal studies In vitro or animal Animal toxicology and/or pharmacology	Human, preclinical, and/or pharmacologic Preclinical/nonclinical data Preclinical/nonclinical studies Preclinical/nonclinical Preclinical/nonclinical toxicology and/or pharmacology
§201.80	In vitro or animal tests In vitro and animal data Serious animal toxicity Animal reproduction studies Studies in animals and humans Animal or human Pertinent animal data Animal Pharmacology and/or Animal Toxicology Animal data Chronic animal toxicity studies	Preclinical/nonclinical tests Preclinical/nonclinical data Serious preclinical/nonclinical toxicity Preclinical/nonclinical reproduction studies Preclinical/nonclinical studies and humans Preclinical/nonclinical or human Pertinent preclinical/nonclinical data Preclinical/nonclinical Pharmacology and or Preclinical/nonclinical Toxicology Preclinical/nonclinical data Chronic preclinical/nonclinical toxicity studies
§202.1	Laboratory animals or in vitro	Preclinical/nonclinical
§312.32	Animal or in vitro studies	Preclinical/nonclinical

[1] 21 C.F.R. §201.80(f)(6)(i)(b) – Teratogenic effects – because of important information regarding the predictability of animal reproductive studies, the following language should not be changed to test-neutral language: "**Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed."** 21 CFR 21 C.F.R. §201.80(f)(6)(i)(c) should also not be changed.

Section	Current language	Proposed test---neutral language
	Findings from animal or in vitro testing Animal or in vitro testing	Findings from preclinical/nonclinical testing Preclinical/nonclinical testing
§312.160	In vitro or in animals	Preclinical/nonclinical
§314.81	Animal study	Preclinical/nonclinical study
§314.200	Animal safety data	Preclinical/nonclinical safety data
§314.430	Animals and humans	Preclinical/nonclinical and humans
§316.20	In vitro laboratory studies, preclinical efficacy studies conducted in an animal model for the human condition…	Preclinical/nonclinicallaboratory studies, preclinical efficacy studies conducted in a model for the human condition
§330.14	Animal toxicology	Preclinical/nonclinical toxicology
§343.80	Animal toxicology	Preclinical/nonclinical toxicology
§361.1	Animal studies	Preclinical/nonclinical studies