agency's authority. This rulemaking is promulgated under the authority described in Subtitle VII, Part A, Subpart I, Section 40103. Under that section, the FAA is charged with prescribing regulations to assign the use of airspace necessary to ensure the safety of aircraft and the efficient use of airspace. This regulation is within the scope of that authority as it establishes Class E airspace extending upward from 700 feet above the surface at OSF St Francis Medical Center Heliport, Ottawa, IL, to support IFR operations.

History

The FAA published an NPRM for Docket No. FAA–2026–8548 in the **Federal Register** (91 FR 46759; July 24, 2026) proposing to establish Class E airspace at OSF St Francis Medical Center Heliport, Ottawa, IL. Interested parties were invited to participate in this rulemaking effort by submitting written comments on the proposal to the FAA. One comment was received, which expressed support for the NPRM.

Incorporation by Reference

Class E airspace designations are published in paragraph 6005 of FAA Order JO 7400.11, Airspace Designations and Reporting Points, which is incorporated by reference in 14 CFR 71.1 on an annual basis. This document amends the current version of that order, FAA Order JO 7400.11M, dated July 30, 2026, and effective September 15, 2026. These amendments will be published in the next update to FAA Order JO 7400.11. FAA Order JO 7400.11M, which lists Class A, B, C, D, and E airspace areas, air traffic service routes, and reporting points, is publicly available as listed in the **ADDRESSES** section of this document.

The Rule

This action modifies 14 CFR part 71 by establishing Class E airspace extending upward from 700 feet above the surface within a 6.8-mile radius of OSF St Francis Medical Center Heliport, Ottawa, IL. This action is the result of instrument procedures being developed for this heliport to support IFR operations.

Regulatory Notices and Analyses

The FAA has determined that this regulation only involves an established body of technical regulations for which frequent and routine amendments are necessary to keep them operationally current. It, therefore: (1) is not a ''significant regulatory action'' under Executive Order 12866; (2) is not a ''significant rule'' under DOT Order 2100.6B, ''Rulemaking and Guidance Procedure'' (March 10, 2025); and (3) is expected to result in, at most, de minimis costs from compliance with applicable operating requirements or minor flight rerouting for operators choosing to navigate around the controlled airspace. Since these amendments are routine and the expected impact to operators is de minimis, the FAA certifies that this rule, when promulgated, does not have a significant economic impact on a substantial number of small entities under the criteria of the Regulatory Flexibility Act.

Environmental Review

The FAA has determined that this action qualifies for categorical exclusion under the National Environmental Policy Act in accordance with FAA Order 1050.1G, ''FAA National Environmental Policy Act Implementing Procedures,'' paragraph B–2.5(a), which categorically excludes from further environmental impact review rulemaking actions that designate or modify classes of airspace areas, airways, routes, and reporting points (see 14 CFR part 71, Designation of Class A, B, C, D, and E Airspace Areas; Air Traffic Service Routes; and Reporting Points); and paragraph B–2.5(k), which categorically excludes from further environmental impact review the publication of existing air traffic control procedures that do not essentially change existing tracks, create new tracks, change altitude, or change concentration of aircraft on these tracks. As such, this action is not expected to result in any potentially significant environmental impacts, and no extraordinary circumstances exist that warrant preparation of an environmental assessment.

Lists of Subjects in 14 CFR 71

Airspace, Incorporation by reference, Navigation (air).

The Amendment

In consideration of the foregoing, the Federal Aviation Administration amends 14 CFR part 71 as follows:

PART 71—DESIGNATION OF CLASS A, B, C, D, AND E AIRSPACE AREAS; AIR TRAFFIC SERVICE ROUTES; AND REPORTING POINTS

■ 1. The authority citation for 14 CFR Part 71 continues to read as follows:

Authority: 49 U.S.C. 106(f), 106(g), 40103, 40113, 40120; E.O. 10854, 24 FR 9565, 3 CFR, 1959–1963 Comp., p. 389.

§ 71.1 [Amended]

■ 2. The incorporation by reference in 14 CFR 71.1 of FAA Order JO 7400.11M, Airspace Designations and Reporting Points, dated July 30, 2026, and effective September 15, 2026, is amended as follows:

Paragraph 6005 Class E Airspace Areas Extending Upward From 700 Feet or More Above the Surface of the Earth.

* * * * *

AGL IL E5 Ottawa, IL [Establish]

OSF St Francis Medical Center Heliport, OH
(Lat. 41°21′30″ N, long 88°49′30″ W)

That airspace extending upward from 700 feet above the surface within a 6.8-mile radius of the OSF St Francis Medical Center Heliport.

* * * * *

Issued in Fort Worth, Texas, on September 18, 2026.

Jerry J. Creecy,

Acting Manager, Operations Support Group, ATO Central Service Center

[FR Doc. 2026–19391 Filed 9–21–26; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 312, 314, 315, 361, and 601

[Docket No. FDA–2026–N–5347]

RIN 0910–AJ27

Nonclinical Testing Terminology

AGENCY: Food and Drug Administration, HHS.

ACTION: Direct final rule.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is issuing a direct final rule that substitutes references to ''animal'' tests or studies with ''nonclinical'' tests or studies, adds a definition of the terms ''nonclinical test'' and ''nonclinical study,'' and makes other comparable or conforming amendments in certain safety and reporting sections of its regulations. The direct final rule also substitutes ''nonclinical'' for ''preclinical'' and ''in vitro'' for consistency in terminology. The Agency is issuing these amendments directly as a final rule because we believe they are noncontroversial changes in terminology that are not expected to affect industry practice and FDA anticipates no significant adverse comments. These amendments align with recent amendments to the Federal

Food, Drug, and Cosmetic Act (FD&C Act) and the Public Health Service Act (PHS Act) and are intended to remove an emphasis, in certain places, on the use of animal testing as the only scientific methodology to assess the safety of a drug in the nonclinical setting. These changes may also foster the development and use of scientifically valid new testing methodologies, potentially improving predictive accuracy of product safety testing while replacing, reducing, or refining animal use. The rule adds no new requirements.

DATES: This rule is effective February 4, 2027. Either electronic or written comments on the direct final rule or its companion proposed rule must be submitted by December 7, 2026. If FDA receives no significant adverse comments within the specified comment period, the Agency intends to publish a document confirming the effective date of the direct final rule in the **Federal Register** within 30 days after the comment period on this direct final rule ends. If timely significant adverse comments are received, the Agency will publish a document in the **Federal Register** withdrawing this direct final rule within 30 days after the comment period on this direct final rule ends.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of December 7, 2026. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2026–N–5347 for ''Nonclinical Testing Terminology.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' We will review this copy, including the claimed confidential information, in our consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

FOR FURTHER INFORMATION CONTACT: Shena Arellano, Office of Policy, Office of Policy, Legislation, and International Affairs, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 301–796–8353.

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I. Executive Summary

A. Purpose of the Direct Final Rule

FDA recognizes that some provisions of its human drug and biological product safety testing and reporting regulations refer only to the use of animal tests where alternatives may be available. FDA is updating these regulations by replacing the terms ''animal test'' and ''animal study'' with ''nonclinical test'' or ''nonclinical study,'' terms which are defined to encompass a broad variety of tests or studies in addition to animal testing, including scientifically valid new approach methodologies (NAMs) that do not use animals. NAMs have the potential to improve predictivity while replacing, reducing, or refining the use of animal testing for evaluating medical product safety. For consistency in terminology, we are also substituting the term ''nonclinical'' for the terms ''preclinical'' and ''in vitro.'' We also replace ''animal'' with ''nonclinical'' in regulations that use the terms ''animal testing,'' ''animal data,'' ''animal findings'' and ''animal models'' to refer to testing, data, findings and models that are performed with, derived from, or made using nonclinical tests or studies.

Because we believe the rule contains noncontroversial changes and we do not expect significant adverse comment on the rulemaking, we are using direct final rulemaking procedures, as described in this document. We are also publishing elsewhere in this issue of the **Federal Register** a companion proposed rule proposing to take the actions described in this direct final rule. The companion proposed rule provides a procedural framework within which the rule may be finalized if the direct final rule is withdrawn because of any significant adverse comments. The comment period for the direct final rule runs concurrently with the comment period for the companion proposed rule. Any comments received in response to the companion proposed rule will be considered as comments regarding the direct final rule.

B. Summary of the Major Provisions of the Direct Final Rule

This direct final rule substitutes the terms ''nonclinical test'' or ''nonclinical study'' for the terms ''animal test, '' ''animal study,'' ''preclinical test,'' and ''in vitro test,'' and makes other comparable or conforming changes in sections addressing human drug and biological product safety and reporting within parts 312, 314, 315, 361 and 601 of Title 21 of the Code of Federal Regulations (21 CFR). It also adds a definition for ''nonclinical test'' and ''nonclinical study'' to part 312 and a definition for ''nonclinical study'' to parts 314, 315, 361, and 601. The definitions are adapted from the definition of ''nonclinical test'' in section 505(z) of the FD&C Act (21 U.S.C. 355(z)).[1]

C. Legal Authority

FDA is issuing this rule under the authority granted to it by the FD&C Act (21 U.S.C. 301 *et seq.*) and the PHS Act (42 U.S.C. 201 *et seq.*). By delegation from the Secretary of the Department of Health and Human Services, FDA is authorized to issue regulations for the efficient enforcement of the FD&C Act (section 701; 21 U.S.C. 371), including provisions addressing the regulation of drug products to ensure their safety and effectiveness, and to regulate biological products to ensure that they are safe, effective, pure, and potent (PHS Act section 351; 42 U.S.C. 262). This direct final rule will help with the efficient enforcement of provisions relating to the following: (1) investigational use of human drugs and biological products and (2) safety of human drugs and biological products.

D. Costs and Benefits

This direct final rule substitutes ''nonclinical'' for ''animal'' in phrases like ''animal test'' and ''animal study;'' substitutes ''nonclinical'' for ''preclinical'' and ''in vitro'' for consistency in terminology; and adds a definition of ''nonclinical test'' and ''nonclinical study'' to the definitions section of several of FDA's drug and biological product regulations. This rule imposes no new requirements on industry and so is expected to generate no costs. The rule may foster the development and use of scientifically valid new testing methodologies and so may yield benefits, but we do not anticipate being able to quantify these benefits. Since this final rule updates terminology to unambiguously allow for a broader range of nonclinical studies to meet current requirements without limiting existing options or imposing new requirements, we conclude this direct final rule is classifiable as an Executive Order 14192 deregulatory action.

II. Direct Final Rulemaking Procedures

In the document titled ''Guidance for FDA and Industry: Direct Final Rule Procedures,'' announced and provided in the **Federal Register** of November 21, 1997 (62 FR 62466), FDA described its procedures on when and how we will employ direct final rulemaking. The guidance may be accessed at *https://www.fda.gov/RegulatoryInformation/Guidances/ucm125166.htm*. We have determined that this rule is appropriate for direct final rulemaking because we believe that it includes only noncontroversial amendments and we anticipate no significant adverse comments. Consistent with our procedures on direct final rulemaking, FDA is also publishing elsewhere in this issue of the **Federal Register** a companion proposed rule with the regulatory amendments described in this direct final rule. The companion proposed rule provides a procedural framework within which the rule may be finalized in the event that the direct final rule is withdrawn because of any significant adverse comments. The comment period for the direct final rule runs concurrently with the comment period for the companion proposed rule. Any comments received in response to the companion proposed rule will be considered as comments regarding the direct final rule.

We are providing a comment period on the direct final rule of 75 days after the date of publication in the **Federal Register**. If we receive any significant adverse comments, we intend to withdraw this direct final rule before its effective date by publication of a notice in the **Federal Register**. A significant adverse comment is defined as a comment that explains why the rule would be inappropriate, including challenges to the rule's underlying

[1] Section 505(z) of the FD&C Act was added by section 3209 of the Food and Drug Omnibus Reform Act of 2022 (FDORA), which was enacted as part of the Consolidated Appropriations Act, 2023. Public Law 117–328, Div. FF, Title III, §§ 3001–3631 (2022).

premise or approach, or would be ineffective or unacceptable without a change. In determining whether an adverse comment is significant and warrants terminating a direct final rulemaking, we will consider whether the comment raises an issue serious enough to warrant a substantive response in a notice-and-comment process. Comments that are frivolous, insubstantial, or outside the scope of the rule will not be considered significant or adverse under this procedure. A comment recommending a regulation change in addition to those in this direct final rule would not be considered a significant adverse comment unless the comment states why the rule would be ineffective without the additional change. In addition, if a significant adverse comment applies to part of this rule and that part can be severed from the remainder of the rule, we may adopt as final those provisions of the rule that are not subject to the significant adverse comment.

If any significant adverse comments are received during the comment period, FDA will publish in the **Federal Register**, before the effective date of this direct final rule, a notice of significant adverse comment and withdraw the direct final rule. If we withdraw the direct final rule, any comments received will be applied to the proposed rule and will be considered in developing a final rule using the usual notice-and-comment procedures.

If FDA receives no significant adverse comments during the specified comment period, FDA intends to publish a document confirming the effective date within 30 days after the comment period ends.

III. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/acronym	What it means
BLA	Biologics License Application.
CFR	Code of Federal Regulations.
DDT	Drug Development Tools.
FD&C Act	Federal Food, Drug, and Cosmetic Act.
FDA or Agency	Food and Drug Administration.
FDORA	Food Drug Omnibus Reform Act.
GST	General Safety Test.
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods.
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.
IND	Investigational New Drug Application.
ISTAND	Innovative Science and Technology Approaches for New Drugs.
MDDT	Medical Device Development Tools.
NAMs	New Approach Methodologies.
NDA	New Drug Application.
OECD	Organisation for Economic Co-operation and Development.
OIRA	Office of Information and Regulatory Affairs.
PDUFA	Prescription Drug User Fee Act.
PHS Act	Public Health Service Act.
U.S.C.	United States Code.

IV. Background

A. Need for the Regulation

Currently, some human drug and biological product regulations refer to animal studies or tests. For example, section 312.88 states that safeguards for patient safety ''include the review of animal studies prior to initial human testing.'' However, the Food and Drug Omnibus Reform Act (FDORA) amended Section 505(i) of the FD&C Act by replacing the term ''preclinical tests (including tests on animals)'' in paragraph (1)(A) and ''animal'' in paragraph (2)(B) with the term, ''nonclinical tests.'' FDORA section 3209(a)(1)–(2). It also added a definition of ''nonclinical test'' to Section 505(z) of the FD&C Act [2] to mean:

[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.

FDORA section 3209(a)(2). FDORA also amended item (bb) of section 351(k)(2)(A)(i)(I) of the PHS Act (42 U.S.C. 262(k)(2)(A)(i)(I)) to replace ''animal studies (including assessment of toxicity)'' with ''an assessment of toxicity (which may rely on, or consist of, a study or studies described in item (aa) or (cc)).'' The studies described in items (aa) and (cc) include analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and clinical studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency under certain conditions of use.

This direct final rule aligns the terminology used in FDA's drug and biological product regulations more closely with the FD&C Act amendments made by FDORA and with the growing prevalence and capabilities of NAMs.

B. FDA's Current Regulatory and Policy Framework

FDA's current regulatory framework generally allows and encourages the use of non-animal testing, including NAMs, as communicated through regulations, guidance, recognition of international standards, and participation with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).

In general, drugs and biological products may only be tested in or on humans if their use in this context complies with part 312, which implements section 505(i) of the FD&C Act (21 U.S.C. 355(i)) and section 351(a)(3) of the PHS Act (42 U.S.C. 262(a)(3)). These regulations aim to

[2] Two subsecs. (z) have been enacted in Section 505. Both were enacted in the Consolidated Appropriations Act, 2023 (Pub. L. 117–328).

ensure that these products are reasonably safe for use in or on humans under the conditions described in the proposed clinical investigations. The clinical investigations may in turn serve to provide evidence as to whether the medical product is safe and effective as part of a marketing application to FDA.

Generally, a person seeking to market a new drug must submit to FDA a new drug application (NDA) with full reports of investigations, including clinical investigations that show whether the drug is safe and effective (21 U.S.C. 355(b)). Generally, a person seeking to market a new biological product must submit to FDA a biologics license application (BLA), which generally includes data derived from nonclinical laboratory and clinical studies demonstrating the product meets prescribed requirements of safety, purity, and potency (§ 601.2(a)).

FDA encourages the use of innovative approaches to safety testing that may provide predictive data for medical products in our review process, including through guidance documents. The Agency explains in guidance documents, such as those included as references in this direct final rule (Refs. 1–16), our support for moving away from animal testing—and encourages parties to contact us to discuss alternative testing methods early on in their development plans. FDA guidances may be accessed at *https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch*.

In addition to guidance, FDA has signaled its support for alternatives to animal testing in other contexts. In a 2015 final rule, FDA removed the codified general safety test (GST) requirements for biological products, which required rodent testing, because the regulations were duplicative of safety test requirements set forth in approved BLAs for products that present specific safety concerns. In that rule, we noted that the ''elimination of the codified GST regulations would encourage the implementation of the principles of the '3Rs,' to reduce, refine, and replace animal use in testing'' while continuing to ensure the safety of biological products using appropriate and specific test methods identified in the product's approved BLA or supplement BLA. (80 FR 37971 at 37972).

In December of 2017, FDA published a roadmap for integrating emerging predictive toxicology methods and new technologies into regulatory safety and risk assessments to potentially reduce the use of animal testing (Ref. 17). This work includes collaborating with ICH, ICCVAM, and the Organisation for Economic Co-operation and Developments (OECD) Test Guidelines Programme.

Section 507 of the FD&C Act requires establishment of a process for the qualification, based on scientific merit, of drug development tools for a proposed context of use; once qualified, any sponsor can then use the tool(s) in the development and evaluation of their products within the qualified context of use. FDA is making use of the Drug Development Tools (DDT) and Innovative Science and Technology Approaches for New Drugs (ISTAND) programs to evaluate, validate, and qualify various tools, including NAMs. DDT and ISTAND submissions include new biomarkers, clinical assessments, animal models for use with the Animal Rule, and other novel approaches or methodologies of potential benefit to drug development and evaluation. These programs support innovation and regulatory science and foster early communication and collaboration with FDA and sponsors helping to bridge the gap between the research of medical products and their delivery to patients.

Sponsors may contact the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) to request feedback on their development programs, the use of nonclinical tests, and feedback on the use of a NAM for a particular development program, such as through a Type D meeting.[3] Alternatively, if a sponsor seeks feedback on the use of a novel manufacturing method that incorporates use of a NAM to support multiple products, the sponsor could consider engaging the CBER Advanced Technologies Team.

A 2024 report to the Science Board to FDA from its New Alternative Methods Subcommittee, entitled ''Potential Approaches to Drive Future Integration of New Alternative Methods for Regulatory Decision-Making'' (Ref. 19), noted that FDA has accepted approaches that reduce the number of animals used in test protocols, including by adopting and issuing ICH guidances that recommend testing of relevant species (ICH S6), that reduce or eliminate animal testing recommendations for reproductive toxicology (ICH S5(R3)) and carcinogenicity testing (ICH S1B(R1)), and that reduce the duration of recommended chronic toxicology studies for oncology indications (ICH S9). The report also noted that FDA has explored options like the use of virtual control groups to support a reduction of animals in studies, and that newer methods are largely already available at FDA to produce scientifically valid data to meet FDA's regulatory needs, including those using systems biology, engineered biologically active tissues, in silico methods, alternative organisms such as Zebrafish and C. *elegans,* and microphysiological systems, including organs-on-chips.

FDA, along with a number of other federal regulatory agencies and research laboratories, participated in the development of the 2024 ICCVAM report entitled ''Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies'' (Ref 20). ICCVAM developed the report to help developers and end users build confidence in NAMs. It recommends the implementation of flexible, fit-for-purpose validation strategies that consider the intended application of the NAM, and describes concepts such as context of use, biological relevance, and technical characterization of NAMs.

In April 2025, FDA announced a roadmap to reduce animal testing in safety studies by replacing them in a stepwise approach with scientifically valid NAMs (Ref. 21). The approach outlined in the roadmap is designed to improve drug safety and identify more efficient methods to inform the evaluation process while reducing animal experimentation. The roadmap provided an overview of key NAM categories and their applicability to drug development and laid out a stepwise list of specific actions FDA is considering for validation and integration of NAMs into its regulatory process, initially focusing on safety testing of monoclonal antibodies.

Although the Agency is optimistic that fostering the use of scientifically valid NAMs will lead to a reduced need for animal testing and to the use of fewer animals and of animals lower on the phylogenetic scale, it is also important to recognize that there remain areas where animal testing is important and necessary. For example, for a product inhibiting a novel molecular target, animal studies may enable the evaluation of toxicities that occur through complex physiologic interactions such as the release of hormones, neurotransmitters, cytokines, and other internally secreted chemicals that maintain homeostasis within an

[3] A Type D meeting is a type of formal meeting described in the Prescription Drug User Fee Act (PDUFA) Commitment letter (Ref. 18) and the August 2026 guidance on Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (Ref. 15). A Type D meeting is focused on a narrow set of issues (*e.g.,* often one, but typically not more than two issues and associated questions). In addition, the issue should not require input from more than 3 disciplines or Divisions.

organism and communication between organ systems. However, we also recognize that NAMs using human-derived cells may be able to assess additional or more relevant endpoints for clinical drug development. Thus, it is important that developers consult with FDA about their use of NAMs, including providing information about the technical characterization of the NAM and its biological relevance for particular contexts of use. As is its general practice, FDA also will develop guidance to support specific recommendations to sponsors about study design, conduct, and interpretation of NAMs as it gains experience with their use and as data and information become available.

In sum, we believe the changes to the terminology used in FDA regulations described in this direct final rule should foster the development and use of new alternative research methods where feasible while ensuring that nonclinical test methods used in drug and biological product development generate data appropriate for demonstrating the safety of the drug product.

V. Description of the Direct Final Rule

The rule amends certain provisions of FDA's drug and biological product regulations addressing the collection, analysis, submission, reporting, and surveillance of safety and toxicological data.[4] Specifically, this rule:

- Amends § 312.3(b) by adding a definition of the terms ''nonclinical test'' and ''nonclinical study'' and §§ 314.3, 315.2 and 601.31 by adding a definition of the term ''nonclinical study.'' The definitions are adapted from the definition of ''nonclinical test'' in section 3209(a) of FDORA. This change aligns the regulations that use the terms ''nonclinical test'' and ''nonclinical study'' [5] with the amendments made to the FD&C Act and the PHS Act by FDORA. Like the statutory definition, the regulatory definitions we are adding include an illustrative, non-exhaustive list of examples of nonclinical tests and studies. We broadened the definition compared to the statutory definition to include ''study'' because part 312 refers to both tests and studies and parts 314, 315, and 601 generally refer to studies instead of tests. Further, FDA considers nonclinical tests and nonclinical studies to be equivalent for purposes of these requirements and does not believe that these changes result in any substantive differences compared to the definition in section 505(z) of the FD&C Act because both definitions describe the same types of nonclinical data that can be used to satisfy the underlying requirement. The definitions we are adopting in this rule also omit reference to when the nonclinical test or study occurs because the regulations being revised focus on the type of data needed to address the requirement, not on when the nonclinical test or study to generate the data occurs. To include the temporal part of the statutory definition (''a test . . . that occurs before or during the clinical trial phase'') would change the meaning of some of the regulatory provisions being revised to use ''nonclinical study'' or ''nonclinical test''.
- Amends the other regulations specified below by substituting the term ''nonclinical test'' or ''nonclinical study'' for the terms ''animal test,'' ''animal study,'' ''preclinical test,'' and ''in vitro test,'' and making other comparable or conforming changes. These changes result in more consistent and updated terminology that is not unduly focused on animal testing and that encompasses the use of scientifically valid NAMs.
- Where FDA's existing regulations that are being revised under this rule use ''animal'' and ''in vitro'' together to describe the scope of nonclinical testing (such as ''animal or in vitro studies''), FDA has historically treated these paired terms here to encompass all nonclinical testing conducted outside of humans. When these regulations were originally developed, in chemico and in silico methodologies were not widely used and the pairing of ''animal'' and ''in vitro'' reflected the available testing methods that were in common use at the time. As in chemico and in silico methods evolved and became scientifically established, they became more widely used in drug development, results from these nonclinical tests were submitted to the Agency under these same provisions, and FDA accepted such data under these provisions when appropriate. Substituting ''nonclinical'' in instances where ''animal'' and ''in vitro'' are used in conjunction does not in practice expand the scope of data that must be reviewed, submitted, or reported under the affected provisions because the regulatory requirements, in these specific instances, generally focus on the significance or relevance of the information to human safety (*e.g.,* ''all information relevant to the safety of the drug,'' ''findings that suggest a significant risk in humans''), not on the specific methodology used to generate that information. Sponsors have submitted data from in silico, in chemico, and other nonclinical methodologies conducted outside a living organism under the current regulations, consistent with this position.

A. Amendment of Part 312—Investigational New Drug Application

Part 312 lists requirements for an investigational new drug application (IND).

1. Section 312.3(b)

Section 312.3(b) lists definitions in alphabetical order that apply to part 312. We are amending § 312.3(b) by adding, after the definition of ''Marketing application,'' the following definition [6] of the terms ''nonclinical test'' and ''nonclinical study'':

Nonclinical test and *nonclinical study* mean a test or study conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test or study. Such test or study 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 or studies.

2. Section 312.22

Section 312.22 provides general principles of the IND submission. Paragraph 312.22(c) notes that amendments to INDs ''should build logically on previous submissions and should be supported by additional information, including the results of

[4] We determined that certain regulations fall outside the scope of this rule. For example, FDA has regulations under which efficacy data may be provided from studies conducted in carefully vetted animal models because it would not be ethical or feasible to conduct definitive efficacy studies in humans for human drugs and biological products intended to ameliorate or prevent serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic chemical, biological, radiological or nuclear substances. (These regulations, 21 CFR 314 subpart I for drugs and 21 CFR 601 subpart H for biological products, are commonly known as the Animal Rule.) These regulations are specific to the use of animals to provide efficacy data under very limited conditions and are not within the scope of this rule. Similarly, part 316 on orphan drugs is outside the scope of this rule. Any studies in animals to support an orphan-drug designation are generally limited to ''preclinical efficacy studies conducted in an animal model for the human disease or condition.'' 21 CFR 316.20(b)(4). Section 316.20(b)(4) also states that ''[a]nimal toxicology studies are generally not relevant to a request for orphan-drug designation.''

[5] The term ''nonclinical study'' is not a ''nonclinical laboratory study'' which is regulated under 21 CFR part 58 and is outside the scope of this rule.

[6] This definition is adapted from the definition of nonclinical test added to section 505(z) of the FD&C Act (21 U.S.C. 355(z)) by section 3209(a) of FDORA.

animal toxicology studies or other human studies as appropriate.'' We are amending the paragraph by replacing ''animal'' with ''nonclinical.'' This change clarifies that the types of supportive toxicology studies that may be appropriate can include nonanimal studies, highlighting the flexibility inherent in this provision. As with toxicology data from animal studies or other human studies, FDA will examine any toxicological data from nonanimal nonclinical studies to determine whether they adequately support the clinical studies identified in the IND.

3. Section 312.23(a)(3)

Section 312.23 lists requirements for IND content and format, and paragraph (a) lists the elements that the IND must contain and in what order. Paragraph (a)(3) describes what is included in the IND's introductory statement and general investigational plan. Paragraph (a)(3)(iv)(*f*) provides that the plan should include ''any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.'' We are amending the paragraph by replacing the word ''animals'' with the phrase ''nonclinical studies.'' While this change expands the types of studies or tests that may be used to provide the basis for a sponsor to identify ''any risks of particular severity or seriousness'' that a sponsor should anticipate, and thus should be included in the investigational plan, this change does not increase the amount of information needed to meet current requirements because the regulatory change does not impose any requirement to conduct additional tests or studies to identify such risks. This change reflects how there is flexibility in the types of toxicological data that can be used to identify risks to be addressed in the general investigational plan. As with toxicological data from animal studies or prior human studies, FDA will examine any toxicological data from nonanimal nonclinical studies to determine whether they adequately support the clinical studies identified in the IND.

4. Section 312.23(a)(5)(ii)

Section 312.23(a)(5) describes what must be included in the IND's investigator's brochure, when such brochure is required by § 312.55. Section 312.23(a)(5)(ii) requires that there be a ''summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.'' We are amending the regulation by replacing the word ''animals'' with the phrase ''nonclinical studies.'' This change adds flexibility and clarifies that the pharmacological and toxicological effects of the drug that must be included in the IND submission may be derived from a broader range of studies than animal studies. This change does not expand the scope of the submission requirement. The investigator's brochure is intended to inform investigators of information relevant to the safe conduct of the clinical investigation, and the obligation to summarize pharmacological and toxicological effects is grounded in that goal rather than in the methodology used to generate the data. Consistent with this, data from nonclinical studies other than animal studies would be included in the brochure to the extent they are relevant to the safe conduct of the proposed investigation. This change does not impose any new testing requirements. As with pharmacological and toxicological effects derived from animal studies or prior human studies, FDA will examine any pharmacological and toxicological data from nonanimal nonclinical studies to determine whether they adequately support the clinical studies identified in the IND.

5. Section 312.23(a)(5)(iii)

Section 312.23(a)(5) describes what must be included in the IND's investigator's brochure, when such brochure is required by § 312.55. Section 312.23(a)(5)(iii) requires that there be a ''summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.'' As above, we are amending the regulation by replacing the word ''animals'' with the phrase ''nonclinical studies.'' This change provides flexibility and clarifies that the pharmacokinetics and biological disposition of the drug may be derived from a broader range of studies than animal studies. This change does not expand the scope of the submission requirement. The investigator's brochure is intended to inform investigators of information relevant to the safe conduct of the clinical investigation, and the obligation to summarize pharmacological and toxicological effects is grounded in that goal rather than in the methodology used to generate the data. Consistent with this, data from nonclinical studies other than animal studies would be included in the brochure to the extent they are relevant to the safe conduct of the proposed investigation. This change does not impose any new testing requirements. As with pharmacokinetics and biological disposition of the drug derived from animal studies or prior human studies, FDA will examine data from nonanimal nonclinical studies to determine whether they adequately support the clinical studies identified in the IND.

6. Section 312.23(a)(8)

Section 312.23(a)(8) describes what pharmacology and toxicology information must be provided in an IND and the first two sentences of the paragraph state that ''[a]dequate 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 animal and other tests required varies with the duration and nature of the proposed clinical investigations.'' We are amending these two sentences in the regulation by replacing the phrase ''pharmacological and toxicological studies of the drug involving laboratory animals or in vitro'' with the phrase ''nonclinical pharmacological and toxicological studies of the drug'' and replacing ''animal and other tests'' with ''nonclinical tests.'' This change provides flexibility and clarifies that the pharmacological and toxicological studies of the drug may be derived from a broader range of studies than laboratory animal and in vitro studies. As discussed above, FDA has treated the paired terms ''animal'' and ''in vitro'' to encompass all nonclinical testing conducted outside of humans and this change is consistent with that position. Additionally, this change does not mandate what types of studies are performed to generate this information; rather, it requires disclosure in the IND of information about the pharmacological and toxicological studies, regardless of the type of non-clinical study that has generated the information. This is not an increase in burden because FDA already permits the use of non-animal studies to satisfy these requirements where appropriate, this change will not preclude sponsors from using any types of studies that are currently permitted to meet these requirements, and this change does not increase the amount of information required to meet these existing requirements. As with pharmacological and toxicological studies of the drug derived from laboratory animal or in vitro studies, FDA will examine data from other types of nonclinical studies to determine whether they adequately support the clinical studies identified in the IND. The remainder of this paragraph, describing FDA guidance

documents and more detail about the required information to be submitted, is not being amended.

7. Section 312.23(a)(8)(i)

Section 312.23(a)(8)(i) requires that each IND contain a ''section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.'' We are amending the regulation by replacing the word ''animals'' with the phrase ''nonclinical tests.'' This change provides flexibility and clarifies that the pharmacological effects and mechanism(s) of action of the drug, and information on the absorption, distribution, metabolism, and excretion of the drug, if known, may be derived from a broader range of studies than animal studies. It does not mandate what types of studies are performed to generate this information but will require submission in the IND of this information regardless of the type of nonclinical study generating the data. This is not an increase in burden because FDA already permits the use of non-animal studies to satisfy these requirements where appropriate, this change will not preclude sponsors from using any types of studies that are currently permitted to meet these requirements, and this change does not increase the amount of information required to meet these requirements. As with such information derived from animal studies, FDA will examine information from nonanimal nonclinical studies to determine whether they adequately support the clinical studies identified in the IND.

8. Section 312.23(a)(8)(ii)(a)

Section 312.23(a)(8)(ii)(a) requires that the toxicology information in the IND contain an ''integrated summary of the toxicological effects of the drug in animals and in vitro. 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; 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.'' We are amending the regulation by replacing the phrase ''in animals and in vitro'' with the phrase ''based on nonclinical studies'' and replacing the phrase ''and any in vitro studies'' with the phrase ''and any nonclinical studies.'' This change provides flexibility and clarifies that the ''integrated summary of the toxicological effects of the drug'' may be derived from a broader range of studies than animal and in vitro studies. As discussed above, FDA has treated the paired terms ''animal'' and ''in vitro'' in the regulations being amended in this direct final rule to encompass all nonclinical testing conducted outside of humans and this change is consistent with that position. It does not mandate what types of studies are performed to generate this information but continues to require submission in the IND of this information regardless of the type of nonclinical study generating the data. This is not an increase in burden because FDA already permits the use of non-animal studies to satisfy these requirements where appropriate, this change will not preclude sponsors from using any types of studies that are currently permitted to meet these requirements, and this change does not increase the amount of information required to meet these requirements. As with such information derived from animal and in vitro studies, FDA will examine information from other types of nonclinical studies to determine whether they adequately support the clinical studies identified in the IND.

9. Section 312.23(a)(10)(i)

Section 312.23(a)(10)(i) provides that ''[i]f the drug is a psychotropic substance or otherwise has abuse potential,'' then the IND must include ''a section describing relevant clinical studies and experience and studies in test animals.'' We are amending the regulation by replacing the phrase ''clinical studies and experience and studies in test animals'' with the phrase ''clinical and nonclinical studies and experience.'' This change provides flexibility and clarifies that the relevant experience and studies do not have to be limited to that which occurred in humans and test animals, but may include studies and experience using nonclinical tests. It does not mandate what types of studies are performed to generate this information but continues to require submission in the IND of this information regardless of the type of nonclinical study generating the data. This is not an increase in burden because FDA already permits the use of non-animal studies to satisfy these requirements where appropriate, this change will not preclude sponsors from using any types of studies that are currently permitted to meet these requirements, and this change does not increase the amount of information required to meet these requirements. As with clinical studies and experience and studies in test animals, FDA will examine studies and experience from nonanimal nonclinical studies to determine their relevance to support an IND for a drug that is a psychotropic substance or otherwise has abuse potential.

10. Section 312.23(a)(10)(ii)

Section 312.23(a)(10)(ii) provides that if the drug is a radioactive drug, then the IND must include ''sufficient data from 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.'' We are amending the regulation by replacing the word ''animal'' with the word ''nonclinical.'' This change adds flexibility and clarifies that the data sufficient to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject may be obtained from a broader range of studies than animal studies. It does not mandate what types of studies are performed to generate this information but will require submission in the IND of this information regardless of the type of nonclinical study generating the data. We believe that this is not an increase in burden because FDA already permits the use of non-animal studies to satisfy these requirements where appropriate, this change will not preclude sponsors from using any types of studies that are currently permitted to meet these requirements, and this change does not increase the amount of information required to meet these requirements. As with data obtained from animal studies or human studies, FDA will examine any data from nonanimal nonclinical studies to determine whether they allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs of a human subject.

11. Section 312.32(b)

Section 312.32 describes what must be contained in IND safety reporting. Paragraph 312.32(b) requires the sponsor to ''promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.'' We are amending the regulation by replacing

the phrase ''animal or in vitro studies'' with the phrase ''nonclinical studies.'' This change clarifies that ''all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources'' includes information from nonclinical studies. This change does not expand the scope of information sponsors must review under this provision; rather, it clarifies FDA's longstanding position that sponsors are required to review all information relevant to the safety of the drug that the sponsor received or obtained from foreign or domestic sources. The list of specific sources of information to be reviewed is a list of examples and has never been intended to be an exhaustive list of potentially relevant sources of information that should be reviewed by a sponsor. The change from ''animal or in vitro studies'' to the broader term ''nonclinical studies'' better captures that intent by explicitly including modern technologies such as computer modeling and organ chips. This change does not impose any new testing requirements.

12. Section 312.32(c)(1)(iii)

Section 312.32(c) requires a sponsor to notify FDA and all participating investigators ''of potential serious risks, from clinical trials or any other source'' in a safety report provided as soon as possible (but not later than 15 calendar days after the sponsor determines that the information qualifies for reporting under the regulation). Section 312.32(c)(1)(iii) is headed ''Findings from animal or in vitro testing.'' The first sentence of the paragraph states: ''The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure.'' We are amending the regulation by replacing the phrase ''animal or in vitro'' with the word ''nonclinical'' in both the heading and first sentence. This change clarifies FDA's longstanding position that any findings ''from clinical trials or any other source'' (21 CFR 312.32(c)(1)), including non-clinical studies, that suggest a significant risk to humans from exposure to the drug must be reported to FDA, including from modern technologies like computer modeling and organ chips that were not commonly used when the regulation was originally written. The information covered by this provision is critical to FDA's ability to protect human subjects in clinical investigations, as it encompasses data that would ''[o]rdinarily . . . result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.'' This change brings the language up-to-date, consistent with scientific progress and the modernization of testing methods; it does not impose any additional testing requirements.

13. Section 312.32(c)(1)(v)

Section 312.32(c)(1)(v) describes the format in which sponsors must submit IND safety reports and contains the statement ''Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format.'' We are amending the regulation by replacing the phrase ''in vitro, animal'' with ''nonclinical'' in this sentence. This change clarifies FDA's longstanding position that any findings ''from clinical trials or any other source,'' including non-clinical studies, that suggest a significant risk to humans from exposure to the drug must be reported to FDA (and participating investigators) (21 CFR 312.32(c)(1)). Further, this revision conforms section 312.32(c)(1)(v) with the changes made to sections 312.32(b) and 312.32(c)(1)(iii) in describing the format for the IND safety reports required by the remainder of section 312.32(c)(1). It does not impose any additional testing requirements.

14. Section 312.33(b)(6)

Section 312.33(b)(6) requires, as part of annual reports, a summary of information ''obtained during the previous year's clinical and nonclinical investigations,'' including ''[a] list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.'' We are amending the regulation by replacing the phrase ''preclinical studies (including animal studies)'' with ''nonclinical studies'' and replacing ''preclinical findings'' with ''nonclinical findings.'' This change conforms the terminology in this regulation with that used in the rest of part 312, as amended in this rule. Paragraphs (b)(1) through (b)(6) of section 312.33 identify the type and scope of information to be included but the change to paragraph (b)(6) does not change the purpose of the summary section of the annual report to ''bring together data from individual studies and *briefly communicate* what was learned during the past year about the investigational drug's safety and effectiveness'' (75 FR 8819 [emphasis added]). The change does not expand the requirements, because section 312.33(b) already specifies that the summary of information covers both clinical and non-clinical information. Although paragraph (b)(6) specifies ''preclinical'' studies and findings (meaning studies and tests before clinical, that is testing or use in humans), the revision to refer to nonclinical studies and findings leaves out that temporal component because some nonclinical studies may take place after the start of clinical studies. Nonetheless, this section of the annual report is intended to be brief and does not require extensive discussion of all activities during the year. Otherwise, the scope of tests and studies described in this provision is the same. Based on these points, we believe that the change to section 312.33(b) and the scope of the required summary of information in the annual report does not increase burden.

15. Section 312.82

Section 312.82 provides that for ''products intended to treat life-threatening or severely-debilitating illnesses, sponsors may request to meet with FDA-reviewing officials early in the drug development process to review and reach agreement on the design of necessary preclinical and clinical studies.'' We are amending the regulation by replacing ''preclinical'' with ''nonclinical.'' This change conforms the terminology in this regulation with that used in the rest of part 312, as amended in this rule, and reflects the fact that some nonclinical studies may take place after the start of clinical studies. This change also reflects that scientific and regulatory recommendations provided during drug development meetings with sponsors may result in more efficient and robust development programs and that engagement with FDA may occur and be fruitful at multiple stages in drug development.

16. Section 312.82(a)

Section 312.82(a) provides that the ''primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing.'' We are amending the regulation by replacing ''animal'' with ''nonclinical.'' This change provides flexibility and clarifies that the meeting may also be used to review and reach agreement on the design of any nonclinical studies needed to initiate human testing, which

is consistent with FDA's support for moving away from animal testing.

17. Section 312.86

Section 312.86 states that ''FDA may undertake focused regulatory research on critical rate-limiting aspects of the preclinical, chemical/manufacturing, and clinical phases of drug development and evaluation.'' We are amending this paragraph by replacing ''preclinical'' with ''nonclinical.'' This change conforms this regulation with the changes we are making in the rest of part 312 and will better reflect the potential scope of FDA regulatory research.

18. Section 312.88

Section 312.88 states that the safeguards for patient safety incorporated within parts 50, 56, 312, 314 and 600 ''include the review of animal studies prior to initial human testing (§ 312.23).'' We are amending the regulation by replacing ''animal'' with ''nonclinical'' to conform to the changes we are making in section 312.23 and to be more consistent with FDA's support for moving away from animal testing.

B. Amendment of Part 314—Applications for FDA Approval To Market a New Drug

1. Section 314.3(b)

Section 314.3(b) lists definitions of terms in alphabetical order that apply to parts 314 and 320. We are amending the section by adding, after the definition of ''Newly acquired information,'' the following definition of ''nonclinical study'' adapted from the definition of ''nonclinical test'' added to section 505 of the FD&C Act by section 3209(a) of FDORA:

Nonclinical study means a test or study conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test or study. Such a test or study 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 or studies.

This definition varies from the definition added to § 312.3(b) in that it only defines ''nonclinical study'' rather than both ''nonclinical test'' and ''nonclinical study.'' This is because part 314 generally uses the term ''study'' rather than ''test.'' To be consistent in terminology across the provisions in this direct final rule, all definitions list ''animal tests and studies'' as an example of non-clinical studies whether the definition is for ''nonclinical studies'' or ''nonclinical test'' and ''nonclinical study.''

2. Section 314.50(d)(2)

Section 314.50 establishes the content and format of an application, new drug application or NDA. It provides that the NDA is required to contain reports of all investigations of the drug product sponsored by the applicant, and ''all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source.'' Section 314.50(d)(2) requires that an NDA contain a ''section describing, with the aid of graphs and tables, animal and in vitro studies with drug, . . .'' We are amending the regulation by replacing ''animal and in vitro'' with ''nonclinical'' and correcting the typographical error ''with drug'' so that the relevant part of the sentence will read ''nonclinical studies with the drug.'' This change provides flexibility and clarifies that nonclinical studies other than animal or in vitro studies may be used to support the pharmacology and toxicology section of an NDA. As discussed above, FDA has treated the paired terms ''animal'' and ''in vitro'' to encompass all nonclinical testing conducted outside of humans and this change is consistent with that position. Furthermore, it does not specify which types of nonclinical studies must be used and thus does not broaden the testing requirement or impose any additional testing requirements. As with such data and information derived from animal studies, if FDA receives data and information from other types of nonclinical studies, FDA will examine it to determine whether it adequately supports the NDA.

3. Section 314.50(d)(2)(iv)

Section 314.50(d)(2)(iv) requires that the NDA's nonclinical pharmacology and toxicology section include ''Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.'' We are amending this sentence to read: ''Any nonclinical studies of the absorption, distribution, metabolism, and excretion of the drug.'' This change provides flexibility and clarifies that nonclinical studies other than animal studies may be used to provide data and information on the absorption, distribution, metabolism, and excretion of the drug. It does not impose any additional testing requirements. As with such data and information derived from animal studies, if FDA receives data and information from other types of nonclinical studies, FDA will examine it to determine whether it adequately supports the NDA.

4. Section 314.50(d)(4)(ii)

Section 314.50(d)(4)(ii) requires that the microbiology section of an NDA for an anti-infective drug include a ''description of the antimicrobial spectra of the drug, including results of in vitro preclinical studies to demonstrate concentrations of the drug required for effective use.'' We are amending the regulation by replacing the phrase ''in vitro preclinical'' with ''nonclinical.'' This change provides flexibility and clarifies that we will accept additional types of nonclinical studies to support the microbiology section of an NDA for an anti-infective drug. It does not add any testing requirements. As with such information derived from in vitro preclinical studies, if FDA receives data and information from other types of nonclinical studies, FDA will examine it to determine whether it adequately supports the microbiology section of the NDA. We also are correcting a typographical error by replacing ''antimicrobial spectra'' with ''antimicrobial spectrum.''

5. Section 314.50(d)(5)(i)

Section 314.50(d)(5)(i) requires that the clinical data section of the NDA include ''[a]description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the animal pharmacology and toxicology data.'' We are amending the regulation by replacing the word ''animal'' with ''nonclinical''. This change provides flexibility and clarifies that we will accept comparison of the results of the human studies with pharmacology and toxicology data from nonanimal nonclinical studies to support the clinical data section of an NDA. It does not add any testing requirements. As with animal pharmacology and toxicology data, if FDA receives pharmacology and toxicology data from nonanimal nonclinical studies, FDA will examine it to determine whether it adequately supports the NDA.

6. Section 314.50(d)(5)(vi)(*a*)

The first sentence of section 314.50(d)(5)(vi)(*a*) requires the applicant to ''submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data

from epidemiological studies of related drugs.'' We are amending the regulation by replacing the word ''animal'' with ''nonclinical.'' This change clarifies that ''all available information about the safety of the drug product'' includes pertinent nonclinical data not obtained from animals. It does not require that applicants conduct additional studies. It recognizes that there are newer methods of assessing safety and brings the requirements up-to-date, consistent with scientific progress and the modernization of testing methods.

7. Section 314.50(d)(5)(vi)(*b*)

The second sentence of section 314.50(d)(5)(vi)(*b*) requires that an applicant's safety update reports ''include the same kinds of information (from clinical studies, animal studies, and other sources) . . .'' We are amending the regulation by replacing the word ''animal'' with ''nonclinical'' to conform to the amendment we are making to section 314.50(d)(5)(vi)(*a*). This does not expand the requirements because this provision already contemplates including information from sources outside of animal studies through the use of the phrase ''and other sources.'' It recognizes that there are newer methods of assessing safety and brings the requirements up-to-date, consistent with scientific progress and the modernization of testing methods.

8. Section 314.81(b)(2)(v)

Section 314.81(b)(2)(v) requires that the postmarketing annual report of an NDA holder include ''[c]opies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (*e.g.,* mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product.'' The paragraph heading reads, ''Nonclinical laboratory studies.'' We are amending the regulation by replacing the phrase ''toxicological findings in animal studies and in vitro studies (*e.g.,* mutagenicity)'' with ''nonclinical toxicological findings, including, for example, from mutagenicity studies.'' As discussed above, FDA has treated the paired terms ''animal'' and ''in vitro'' to encompass all nonclinical testing conducted outside of humans and this change is consistent with that position. This change does not require NDA holders to conduct new or additional studies. It simply brings the reporting requirements up to date, to capture newer methods of generating toxicological findings, consistent with scientific progress and the modernization of testing methods.

9. Section 314.81(b)(2)(vii)(*a*)(*7*)

Section 314.81(b)(2)(vii)(*a*)(*7*) specifies that the status report of the schedule for completion and reporting of the postmarketing study commitment ''should include the actual or projected dates for submission of the study protocol to FDA, completion of patient accrual or initiation of an animal study, completion of the study, submission of the final study report to FDA, and any additional milestones or submissions for which projected dates were specified as part of the commitment.'' We are amending the regulation by replacing the phrase ''an animal'' with ''a nonclinical.'' This change provides flexibility by recognizing that a postmarketing study commitment may include nonanimal nonclinical studies, and therefore, the status report should include the date for initiation of a nonanimal nonclinical study that is part of a postmarketing study commitment. We note that this obligation to include information in the status report required under section 314.81(b)(2)(vii)(*a*) is limited to postmarketing study commitments and this amendment would not require additional reporting of nonclinical studies that are outside of such commitments.

10. Section 314.93

Section 314.93 describes conditions under which FDA will or will not approve a petition to submit an ANDA for a drug product that is not identical to a listed drug in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one active ingredient in a listed combination drug. Paragraph (e)(1) of section 314.93 lists a series of conditions under which FDA will not approve such a petition, one of which is if it finds that ''[i]nvestigations must be conducted to show the safety and effectiveness of the drug product . . .'' The first sentence of paragraph 314.93(e)(2) states that ''[f]or purposes of this paragraph, 'investigations must be conducted' means that information derived from animal or clinical studies is necessary to show that the drug product is safe or effective.'' We are amending § 314.93(e)(2) by replacing ''animal'' with ''nonclinical.'' This change in terminology does not alter FDA's implementation through regulation of the requirement articulated in section 505(j)(2)(C)(i) that if the Agency finds investigations must be conducted to show safety and effectiveness of the petitioned drug product then it will not approve a petition to submit such an ANDA. It brings the regulation up-to-date, consistent with scientific progress and the modernization of testing methods, by recognizing that when studies are necessary to determine that a drug product is safe or effective, nonclinical methods other than animal studies might be used to make that determination.

11. Section 314.200(d)(3)

Section 314.200 addresses the procedures for issuing a notice of opportunity for a hearing on CDER's proposal to refuse to approve an application or to withdraw the approval of an application or abbreviated application under section 505(e) of the FD&C Act, filing a notice of participation and request for a hearing, and submitting studies and comments. Section 314.200(d) provides that the person requesting a hearing is required to submit certain information on which the person relies to justify a hearing with respect to the drug product and paragraph (d)(3) specifies FDA's preferred format for such submissions. Roman numeral heading I, letter A of that format identifies ''Animal safety data'' as a component of such submissions. FDA is amending the regulation by replacing ''Animal'' with ''Nonclinical.'' This change provides flexibility and clarifies that the safety data in support of the submission may come from nonclinical tests other than animal tests. To the extent that such tests have not been performed or the submitter does not rely on the data to justify a hearing with respect to the drug product, the regulation, including as amended, does not require such tests to be performed or data submitted.

12. Section 314.430(a)

Section 314.430(a) specifies that the safety and effectiveness data for which FDA will determine public availability include ''all studies and tests of a drug on animals and humans'' as well as studies and tests to establish identity, stability, purity, potency, and bioavailability. FDA is amending the regulation by replacing the phrase ''all studies and tests of a drug on animals and humans'' with ''all nonclinical and clinical studies and tests of a drug.'' This change conforms the regulation to the scope of data that may be submitted to support the safety and effectiveness of a drug.

C. Amendment of Part 315—Diagnostic Radiopharmaceuticals

1. Section 315.2

Section 315.2 is the definition section of part 315, with paragraphs (a) and (b) currently defining two types of

diagnostic radiopharmaceuticals. We are amending the section by first redesignating the introductory text as paragraph (a) and redesignating current paragraphs (a) and (b) as paragraphs (a)(1) and (a)(2) such that the two types of diagnostic radiopharmaceuticals are defined in paragraph (a); our amendments include minor revisions to refer to ''paragraph (a)(1)'' rather than ''paragraph (a)'' in the cross-reference in the definition of nonradioactive reagent kit. We are also adding, as a new paragraph (b), the definition of ''nonclinical study'' adapted from the definition of ''nonclinical test'' added to section 505 of the FD&C Act by section 3209(a) of FDORA as follows: (b) For purposes of this part, *nonclinical study* means a test or study conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test or study. Such test or study 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 or studies.

This definition varies from the definition added to § 312.3(b) in that it only defines ''nonclinical study'' rather than both ''nonclinical test'' and ''nonclinical study''. This is because part 315 generally uses the term ''study'' rather than ''test.'' To be consistent in terminology, all definitions list ''animal tests or studies'' as an example of non-clinical studies, whether the definition is for ''nonclinical studies'' or ''nonclinical test'' and ''nonclinical study''.

2. Section 315.6(c)(2)

Section 315.6(c)(2) states that safety data required by FDA for diagnostic radiopharmaceuticals ''may include, but is not limited to, the dose, route of administration, frequency of use, half-life of the ligand or carrier, half-life of the radionuclide, and results of clinical and preclinical studies.'' We are amending the regulation by replacing ''preclinical'' with ''nonclinical.'' This change conforms the terminology in this regulation with the other regulations in this rule; as noted earlier, part of the intent of this rule is to bring more consistency to these regulations in referring to non-clinical tests. This revision does not expand the requirements because the revision is to an example of the type of information that the regulation requires.

3. Section 315.6(d)

Section 315.6(d) states that ''[t]he radiation safety assessment must establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate animal models.'' We are amending the regulation by replacing the phrase ''animal'' with ''nonclinical.'' This change provides flexibility and clarifies that radiation dosimetry evaluations may be conducted in appropriate nonclinical models other than animal models. As with data obtained from animal models and human studies, FDA will examine data from nonanimal nonclinical models to determine whether they support the establishment of a safe radiation dose.

D. Amendment of Part 361—Prescription Drugs for Human Use Generally Recognized as Safe and Effective and Not Misbranded: Drugs Used in Research

1. Section CFR 361.1(d)(7)

Section CFR 361.1(d)(7) states in the second sentence after the heading that a protocol for determining the safety of radioactive drugs to be used for human research ''shall be based upon a sound rationale derived from appropriate animal studies or published literature and shall be of sound design such that information of scientific value may result.'' We are amending the regulation by replacing ''animal studies'' with ''nonclinical studies, as defined in § 312.3(b) of this chapter.'' This change adds flexibility and clarifies that the sound rationale may be derived from appropriate nonclinical studies other than animal studies. As with animal studies, FDA will examine information from nonanimal nonclinical studies to determine if it supports a sound rationale for the use of the radioactive drugs in human research.

E. Amendment of Part 601—Licensing

1. Section 601.31

Section 601.31 establishes definitions for certain terms used in part 601, with paragraphs (a) and (b) currently defining two types of diagnostic radiopharmaceuticals. We are amending the section by first redesignating the introductory text as paragraph (a) and redesignating current paragraphs (a) and (b) as paragraph (a)(1) and (a)(2) such that the two types of diagnostic radiopharmaceuticals are defined in paragraph (a); our amendments include minor revisions to refer to ''paragraph (a)(1)'' rather than ''paragraph (a)'' in the cross-reference in the definition of nonradioactive reagent kit. We are adding, as a new paragraph (b), the definition of ''nonclinical study'' adapted from the definition of ''nonclinical test'' added to section 505 of the FD&C Act by section 3209(a) of FDORA as follows:

(b) For purposes of this part, *nonclinical study* means a test or study conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test or study. Such test or study 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 or studies.

This definition varies from the definition added to § 312.3(b) in that it only defines ''nonclinical study'' rather than both ''nonclinical test'' and ''nonclinical study.'' This is because part 601 generally uses the term ''study'' rather than ''test.'' To be consistent in terminology, all definitions list ''animal tests or studies'' as an example of non-clinical studies, whether the definition is for ''nonclinical studies'' or ''nonclinical test'' and ''nonclinical study.''

2. Section 601.35(c)(2)

Section 601.35(c)(2) states that safety data required by FDA for diagnostic radiopharmaceuticals ''may include, but is not limited to, the dose, route of administration, frequency of use, half-life of the ligand or carrier, half-life of the radionuclide, and results of clinical and preclinical studies.'' We are amending the regulation by replacing ''preclinical'' with ''nonclinical.'' This change conforms the terminology in this regulation with that used in its counterpart regulation section 315.6(c)(2); as noted earlier, part of the intent of this rule is to bring more consistency to these regulations in referring to non-clinical tests.

3. Section 601.35(d)

Section 601.35(d) states that ''[t]he radiation safety assessment must establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate animal models.'' We are amending the regulation by replacing ''animal'' with ''nonclinical.'' This change conforms the terminology in this regulation with that used in its counterpart regulation section 315.6(d) and is being made for the same reasons; as noted earlier, part of the intent of this rule is to bring more

consistency to these regulations in referring to non-clinical tests.

4. Section 601.70(b)(7)

Section 601.70(b)(7) states that the schedule of a BLA holder's completion and reporting of a postmarketing study commitment in the holder's annual progress report ''should include the actual or projected dates for submission of the study protocol to FDA, completion of patient accrual or initiation of an animal study, completion of the study, submission of the final study report to FDA, and any additional milestones or submissions for which projected dates were specified as part of the commitment.'' We are amending the regulation by replacing the phrase ''an animal'' with ''a nonclinical'' in this provision. This change provides flexibility by recognizing that a postmarketing study commitment may include nonanimal nonclinical studies, and therefore, the status report should include the date for initiation of a nonanimal nonclinical study that is part of a postmarketing study commitment. We note that this obligation to include information in the status report required under section 601.70(b)(8) is limited to postmarketing studies described in 21 CFR 601.70(a) and this amendment would not require additional reporting of nonclinical studies that are outside of such commitments.

VI. Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the direct final rule under Executive Order 12866, Executive Order 13563, Executive Order 14192, the Regulatory Flexibility Act (5 U.S.C. 601–612), the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act (5 U.S.C. 801, Pub. L. 104–121), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4).

Executive Orders 12866 and 13563 direct us to assess all benefits and costs of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits. The Office of Information and Regulatory Affairs (OIRA) has determined that this direct final rule is a significant regulatory action under section 3(f) of Executive Order 12866.

Executive Order 14192 requires that any new incremental costs associated with certain significant regulatory actions ''shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least 10 prior regulations.'' This direct final rule is classifiable as an Executive Order 14192 deregulatory action.

Because this rule is not likely to result in an annual effect on the economy of $100 million or more or to meet other criteria specified in the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act, OIRA has determined that this rule does not fall within the scope of 5 U.S.C. 804(2).

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because we estimate that this direct final rule will produce no quantifiable costs, we certify that this direct final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes estimates of anticipated impacts, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $193 million, using the most current (2025) Implicit Price Deflator for the Gross Domestic Product. This direct final rule will not result in an expenditure in any year that meets or exceeds this amount.

B. Overview of Benefits, Costs, and Transfers

This direct final rule substitutes ''nonclinical'' for ''animal'' in phrases like ''animal test,'' substitutes ''nonclinical'' for ''preclinical'' and ''in vitro'' for consistency in terminology, and adds a definition of ''nonclinical test'' and ''nonclinical study'' to the definitions section of FDA's drug and biological product regulations. Nonclinical tests and studies include but are not limited to the following: cell-based assays, organ chips and microphysiological systems, computer modeling, other nonhuman or human biology-based test methods (*e.g.,* bioprinting), and animal tests or studies. FDA already permits the use of nonanimal studies and this rule will not preclude sponsors from using any types of studies that are currently permitted; industry will continue to provide information on the nonanimal studies that they use and rely on. The terminology changes in this rule also address existing obligations to submit and report information on nonclinical testing to FDA. Where the rule substitutes the term ''nonclinical'' for the paired terms ''animal'' and ''in vitro,'' this change does not expand the scope of data that must be reviewed, submitted, or reported, because FDA has historically treated those paired terms in the context of the regulations being amended in this direct final rule to encompass all nonclinical testing conducted outside of humans. These regulatory requirements generally focus on the significance or relevance of the information to human safety rather than on the methodology used to generate it. As described in section V of this rule, sponsors have submitted data from in silico, in chemico, and other nonclinical methodologies under the current regulations consistent with this position and FDA has accepted such data under these provisions when appropriate. In short, this rule imposes no new requirements on industry and so is expected to generate no costs. Hence, we estimate that this direct final rule will produce no quantifiable savings, costs, or transfers. We do not expect any loss of public health benefits as a result of this rule. In fact, this direct final rule may foster the development and use of scientifically valid non-animal methods and so may yield benefits from this added flexibility.

Table 1 summarizes the estimated benefits and costs of the direct final rule using a 10-year time horizon. We estimate that annualized benefits would be $0 million per year using either a 3 or 7 percent discount rate and that annualized costs would be $0 million per year using either a 3 or 7 percent discount rate.

TABLE 1—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF THE DIRECT FINAL RULE
[Millions of 2025 dollars]

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered	
Benefits:							
Annualized Monetized ($millions/year)	$0	$0	$0	2025	7	2025–2034	
	0	0	0	2025	3	2025–2034	
Annualized Quantified	.....	.....	.....	.....	7	.....	
	.....	.....	.....	.....	3	.....	
Qualitative	The rule may foster the development and use of scientifically valid new testing methodologies.						
Costs:							
Annualized Monetized ($millions/year)	0	0	0	2025	7	2025–2034	
	0	0	0	2025	3	2025–2034	
Annualized Quantified	.....	.....	.....	.....	7	.....	
	.....	.....	.....	.....	3	.....	
Qualitative.							
Transfers:							
Federal Annualized Monetized ($millions/year)	.....	.....	.....	.....	7	.....	
	.....	.....	.....	.....	3	.....	
	From:			To:			
Other Annualized Monetized ($millions/year)	.....	.....	.....	.....	7	.....	
	.....	.....	.....	.....	3	.....	
	From:			To:			

Effects:
State, Local or Tribal Government: None.
Small Business: None.
Wages: None.
Growth: None.

This direct final rule addresses provisions in human drug and biological product regulations that refer to animal studies or tests. It implements updates to definitions based on new statutory provisions enacted in the Consolidated Appropriations Act, 2023 (Pub. L. 117–328) that unambiguously allow for a broader range of nonclinical studies to meet current requirements without imposing new requirements. Prior to legislative action, some sponsors likely relied on existing terminology in codified regulations that emphasized the use of animal testing as the only scientific methodology to assess the safety of a drug in the nonclinical setting. Adopting a pre-statutory baseline for analysis, we anticipate that this direct final rule will serve as an enabling action that results in an incremental shift by some sponsors from animal testing to other types of nonclinical testing, when appropriate. Under the new definition, some sponsors will shift to other methods, including those enumerated in a new definition of ''nonclinical test'': (1) cell-based assays; (2) organ chips and microphysiological systems, (3) computer modeling, and (4) other nonhuman or human biology-based test methods, such as bioprinting; or they may continue to pursue the methods emphasized in the baseline scenario of (5) animal tests or studies. Because the rule updates terminology to unambiguously allow for a broader range of nonclinical studies to meet current requirements without limiting existing options or imposing new requirements, it is classified as a deregulatory action under Executive Order 14192.

In line with Executive Order 14192, in Table 2 we estimate present and annualized values of costs, cost savings, and net costs over a perpetual time horizon. We estimate that this direct final rule would generate $0 million per year in annualized net cost savings at a 7 percent discount rate, discounted relative to year 2024 over a perpetual time horizon. Since this final rule updates terminology to unambiguously allow for a broader range of nonclinical studies to meet current requirements without limiting existing options or imposing new requirements, we conclude this direct final rule is classifiable as an Executive Order 14192 deregulatory action.

TABLE 2—EXECUTIVE ORDER 14192 SUMMARY TABLE
[Millions of 2025 dollars, discounted over a perpetual time horizon relative to year 2024 at a 7 percent discount rate]

	Primary estimate	Low estimate	High estimate
Present Value of Costs	$0	$0	$0
Present Value of Cost Savings	0	0	0
Present Value of Net Costs	0	0	0
Annualized Costs	0	0	0
Annualized Cost Savings	0	0	0
Annualized Net Costs	0	0	0

VII. Analysis of Environmental Impacts

We have determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Paperwork Reduction Act of 1995

FDA concludes that this direct final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3521) is not required.

IX. Federalism

We have analyzed this direct final rule in accordance with the principles set forth in Executive Order 13132. We have determined that this direct final rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

X. Consultation and Coordination With Indian Tribal Governments

We have analyzed this direct final rule in accordance with the principles set forth in Executive Order 13175. We have determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes.

XI. References

The following references are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *https://www.regulations.gov.* FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

1. FDA guidance for industry ''S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals,'' May 2012, available at *https://www.fda.gov/media/78034/download.*
2. FDA guidance for industry ''S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use,'' June 2012, available at *https://www.fda.gov/media/71980/download.*
3. FDA guidance for industry ''S3A Guidance: Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies: Focus on Microsampling, Questions and Answers,'' May 2018, available at *https://www.fda.gov/media/100027/download.*
4. FDA guidance for industry ''S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, Questions and Answers,'' June 2018, available at *https://www.fda.gov/media/100344/download.*
5. FDA guidance for industry ''Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations,'' August 2018, available at *https://www.fda.gov/media/107641/download.*
6. FDA guidance for industry ''Testicular Toxicity: Evaluation During Drug Development,'' October 2018, available at *https://www.fda.gov/media/117948/download.*
7. FDA guidance for industry ''Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations,'' May 2019, available at *https://www.fda.gov/media/124829/download.*
8. FDA guidance for industry ''Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations,'' August 2019, available at *https://www.fda.gov/media/129547/download.*
9. FDA guidance for industry ''Long Term Follow-Up After Administration of Human Gene Therapy Products,'' January 2020, available at *https://www.fda.gov/media/113768/download.*
10. FDA guidance for industry ''Human Gene Therapy for Hemophilia,'' January 2020, available at *https://www.fda.gov/media/113799/download.*
11. FDA guidance for industry ''Human Gene Therapy for Retinal Disorders,'' January 2020, available at *https://www.fda.gov/media/124641/download.*
12. FDA guidance for industry ''Human Gene Therapy for Rare Diseases,'' January 2020, available at *https://www.fda.gov/media/113807/download.*
13. FDA guidance for industry ''S9 Nonclinical Evaluation for Anticancer Pharmaceuticals,'' March 2010, available at *https://www.fda.gov/media/73161/download.*
14. FDA guidance for industry ''S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals,'' May 2021, available at *https://www.fda.gov/media/148475/download.*
15. FDA guidance for industry ''Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products,'' August 2026, available at *https://www.fda.gov/media/172311/download.*
16. FDA draft guidance for industry ''General Considerations for the Use of New Approach Methodologies in Drug Development,'' March 2026, available at *https://www.fda.gov/media/191589/download.*
17. FDA ''Predictive Toxicology Roadmap,'' December 2017, available at *https://www.fda.gov/files/science%20&%20research/published/FDA's-Predictive-Toxicology-Roadmap.pdf.*
18. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 through 2027 (Commitment Letter), available at *https://www.fda.gov/media/151712/download.*
19. Report to the Science Board to FDA ''Potential Approaches to Drive Future Integration of New Alternative Methods for Regulatory Decision-Making,'' October 2024, available at *https://www.fda.gov/media/182478/download.*
20. ICCVAM ''Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies,'' March 2024, available at *https://ntp.niehs.nih.gov/sites/default/files/2024-03/VWG_Report_27Feb2024_FD_508.pdf.*
21. FDA ''Roadmap to Reducing Animal Testing in Preclinical Safety Studies,'' April 2025, available at *https://www.fda.gov/media/186092/download?attachment.*

List of Subjects

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 315

Biologics, Drugs.

21 CFR Part 361

Medical research, Prescription drugs, Radiation protection.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 312, 314, 315, 361, and 601 are amended as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

■ 1. The authority citation for part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360bbb, 371; 42 U.S.C. 262.

■ 2. In § 312.3, amend paragraph (b), by adding in alphabetical order the definition for ''nonclinical test and nonclinical study'' to read as follows:

§ 312.3 Definitions and interpretations.

* * * * *

(b) * * *

Nonclinical test and *nonclinical study* mean a test or study conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test or study. Such test or study 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 or studies.

* * * * *

§ 312.22 [Amended]

■ 3. In § 312.22, amend paragraph (c) in the second sentence by removing the word ''animal'' and adding in its place the word ''nonclinical''.

■ 4. Amend § 312.23 by:

■ a. In paragraph (a)(3)(iv)*(f),* removing the word ''animals'' and adding in its place the phrase ''nonclinical studies'';

■ b. In paragraphs (a)(5)(ii) and (iii), removing the word ''animals'', wherever it appears, and adding in its place the phrase ''nonclinical studies'';

■ c. Revising paragraph (a)(8);

■ d. In paragraph (a)(10)(i), removing the phrase ''clinical studies and experience and studies in test animals'' and adding in its place the phrase ''clinical and nonclinical studies and experience''; and

■ e. In paragraph (a)(10)(ii), removing the word ''animal'' and adding in its place the word ''nonclinical''.

The revisions read as follows:

§ 312.23 IND content and format.

(a) * * *

(8) *Pharmacology and toxicology information.* Adequate information about nonclinical pharmacological and toxicological studies of the drug, 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 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.

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

(ii) *Toxicology.* (A) An integrated summary of the toxicological effects of the drug based on nonclinical studies. 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; 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 nonclinical studies intended to evaluate drug toxicity.

(B) For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review.

* * * * *

§ 312.32 [Amended]

■ 5. Amend § 312.32 by:

■ a. In paragraph (b), removing the phrase ''animal or in vitro studies'' and adding in its place the phrase ''nonclinical studies'';

■ b. In paragraph (c)(1)(iii), removing the phrase ''animal or in vitro'', wherever it appears, and adding in its place the word ''nonclinical''; and

■ c. In paragraph (c)(1)(v), removing the phrase ''in vitro, animal'', wherever it appears, and adding in its place the word ''nonclinical''.

§ 312.33 [Amended]

■ 6. In § 312.33, amend paragraph (b)(6) by:

■ a. Removing the phrase ''preclinical studies (including animal studies)'' and adding in its place the phrase ''nonclinical studies''; and

■ b. Removing the phrase ''preclinical findings'' at the end of the sentence and adding in its place the phrase ''nonclinical findings''.

§ 312.82 [Amended]

■ 7. Amend § 312.82 by:

■ a. Removing the word ''preclinical'' and adding in its place the word ''nonclinical''; and

■ b. Removing the word ''animal'' and adding in its place the word ''nonclinical''.

§ 312.86 [Amended]

■ 8. Amend § 312.86 by removing the word ''preclinical'' and adding in its place the word ''nonclinical''.

§ 312.88 [Amended]

■ 9. Amend § 312.88 by removing the word ''animal'' and adding in its place the word ''nonclinical''.

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

■ 10. The authority citation for part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 355f, 356, 356a, 356b, 356c, 356e, 360cc, 360ddd, 360ddd–1, 371, 374, 379e, 379k–1.

■ 11. In § 314.3, amend paragraph (b), by adding in alphabetical order the definition for ''nonclinical study'' to read as follows:

§ 314.3 Definitions.

* * * * *

(b) * * *

Nonclinical study means a test or study conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test or study. Such test or study 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 or studies.

* * * * *

§ 314.50 [Amended]

■ 12. Amend § 314.50 by:

■ a. In paragraph (d)(2) introductory text, removing the phrase ''animal and in vitro studies with drug'' and adding in its place the phrase ''nonclinical studies with the drug'';

■ b. In paragraph (d)(2)(iv), adding the word ''nonclinical'' before the word ''studies'', and removing the phrase ''in animals'' at the end of the sentence;

■ c. In paragraph (d)(4)(ii), removing the word ''spectra'' and adding in its place the word ''spectrum'', and removing the phrase ''in vitro preclinical'' and adding in its place the word ''nonclinical'';

■ d. In paragraph (d)(5)(i), removing the word ''animal'' and adding in its place the word ''nonclinical'';

■ e. Redesignating paragraphs (d)(5)(vi)(*a*) and (d)(5)(vi)(*b*) as

paragraphs (d)(5)(vi)(A) and (d)(5)(vi)(B);
■ f. In newly redesignated paragraph (d)(5)(vi)(A), removing the word ''animal'' in paragraph (*a*) and adding in its place the word ''nonclinical''; and
■ g. In newly redesignated paragraph (d)(5)(vi)(B), removing the word ''animal'' in paragraph (*b*) and adding in its place the word ''nonclinical''.

§ 314.81 [Amended]

■ 13. Amend § 314.81 by:
■ a. In paragraph (b)(2)(v), removing the phrase ''toxicological findings in animal studies and in vitro studies (*e.g.,* mutagenicity)'' and adding in its place the phrase ''nonclinical toxicological findings, including, for example, from mutagenicity studies''; and
■ b. In paragraph (b)(2)(vii)(*a*)(*7*), removing the phrase ''an animal'' and adding in its place the phrase ''a nonclinical''.

§ 314.93 [Amended]

■ 14. In § 314.93, amend paragraph (e)(2) by removing the word ''animal'' and adding in its place the word ''nonclinical''.

§ 314.200 [Amended]

■ 15. In § 314.200, in the analysis format in paragraph (d)(3), amend the heading for item I.A. by removing the word ''Animal'' and adding in its place the word ''Nonclinical.''

§ 314.430 [Amended]

■ 16. In § 314.430, amend paragraph (a) by removing the phrase ''all studies and tests of a drug on animals and humans'' and adding in its place the phrase ''all nonclinical and clinical studies and tests of a drug''.

PART 315—DIAGNOSTIC RADIOPHARMACEUTICALS

■ 17. The authority citation for part 315 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 371, 374, 379e; sec. 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

■ 18. Revise § 315.2 to read as follows:

§ 315.2 Definitions.

(a) For purposes of this part, *diagnostic radiopharmaceutical* means:
(1) 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
(2) Any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such article as defined in paragraph (a)(1) of this section.
(b) For purposes of this part, *nonclinical study* means a test or study conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test or study. Such test or study 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 or studies.

§ 315.6 [Amended]

■ 19. Amend § 315.6 by:
■ a. In paragraph (c)(2), removing the word ''preclinical'' and adding in its place the word ''nonclinical''; and
■ b. In paragraph (d), removing the word ''animal'' and adding in its place the word ''nonclinical''.

PART 361—PRESCRIPTION DRUGS FOR HUMAN USE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED: DRUGS USED IN RESEARCH

■ 20. The authority citation for part 361 continues to read as follows:

Authority : 21 U.S.C. 321, 351, 352, 353, 355, 371; 42 U.S.C. 262.

§ 361.1 [Amended]

■ 21. In § 361.1, amend paragraph (d)(7) by removing the phrase ''animal studies'' and adding in its place the phrase ''nonclinical studies, as defined in § 312.3(b) of this chapter''.

PART 601—LICENSING

■ 22. The authority citation for part 601 continues to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note), sec 7002(e), Pub. L. 111–148, 124 Stat. 817, as amended by sec. 607, Division N, Pub. L. 116–94, 133 Stat. 3127.

■ 23. Revise § 601.31 is amended to read as follows:

§ 601.31 Definitions.

(a) For purposes of this part, *diagnostic radiopharmaceutical* means:
(1) 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
(2) Any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such article as defined in paragraph (a)(1) of this section.
(b) For purposes of this part, *nonclinical study* means a test or study conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test or study. Such test or study 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 or studies.

§ 601.35 [Amended]

■ 24. Amend § 601.35 by:
■ a. In paragraph (c)(2), removing the word ''preclinical'' and adding in its place the word ''nonclinical''; and
■ b. In paragraph (d), removing the word ''animal'' and adding in its place the word ''nonclinical''.

§ 601.70 [Amended]

■ 25. In § 601.70, amend paragraph (b)(7) by removing the phrase ''an animal'' and adding in its place the phrase ''a nonclinical''.

Robert F. Kennedy, Jr.,

Secretary, Department of Health and Human Services.

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FEDERAL COMMUNICATIONS COMMISSION

47 CFR Part 73

[MB Docket Nos. 19–310, 17–105; FCC 24–66; FR ID 368194]

Reinstatement of Radio Non-Duplication Rule for Commercial FM Stations; Correction

AGENCY: Federal Communications Commission.

ACTION: Correcting amendment.

SUMMARY: This document corrects the final rule portion of a **Federal Register** document published on July 3, 2024. That document inadvertently included an error in a section heading of regulatory text. This document corrects the final regulations.

DATES: Effective on September 22, 2026.

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SUPPLEMENTARY INFORMATION: This document corrects the final rule document published at 89 FR 55078,