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Nonclinical Testing Rulemaking Update: FDA Encourages Adoption of NAMs Over Animal Tests

On September 22, 2026, the U.S. Food and Drug Administration (FDA) issued a direct final rule that substitutes "nonclinical" tests or studies for "animal" tests or studies and makes other conforming terminology changes. For example, the rule substitutes "nonclinical" for "preclinical" and standardizes the use of "in vitro." The rule adds no new requirements but aims to align with the agency's directives to eliminate animal studies as the sole scientific methodology to assess the safety of a drug in a nonclinical setting.

The FDA recognizes that its regulations need to be updated because some provisions of its human drug and biological product safety testing and reporting regulations only refer to animal tests when nonanimal alternatives known as new approach methodologies (NAMs) are available for preclinical testing. Some of those nonanimal-based NAMs include cell-based assays, organ chips and microphysiological systems, computer modeling, and other nonhuman or human biology-based test methods such as bioprinting.

Sponsors may contact the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research to request feedback on the use of a NAM for a particular development program, for example, through a Type D meeting. A Type D meeting is focused on a narrow set of issues – generally no more than two – and related questions. Alternatively, a sponsor may receive feedback on the use of a NAM in a novel manufacturing method by engaging CBER's Advanced Technologies Team.

In 2024, FDA issued a report from its NAM Subcommittee, Potential Approaches to Drive Future Integration of New Alternative Methods for Regulatory Decision-Making,

that discusses how the FDA, along with the International Council for Harmonisation, is exploring ways to reduce the number of animals used in test protocols, including in various toxicology tests. Here, the rule identifies potential NAMs, including virtual control groups that reduce the number of animals used in studies, as well as engineered biologically active tissues, in silico methods, alternative organisms such as zebrafish and *C. elegans*, and microphysiological systems, including organs-on-chips.

The FDA, along with several other federal regulatory agencies and research organizations, developed a 2024 report, Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies, to help developers and end users build confidence in NAMs. The report recommends the implementation of flexible, fit-for-purpose NAMs for the intended use. FDA now believes that the use of scientifically valid NAMs will lead to a reduced need for animal testing through the use of fewer animals and animals lower on the phylogenetic scale. In addition, NAMs using human-derived cells may be able to assess additional or more relevant endpoints for clinical drug development.

The FDA also noted that certain regulations fall outside this rule. In particular, certain drugs and biologics used to treat diseases for which efficacy studies in humans would be unethical or infeasible are outside the scope of the rule. These include products studied for use against lethal or permanently disabling toxic chemical, biological, radiological, or nuclear substances. In addition, some orphan drug designations require preclinical efficacy studies in animal models to support an orphan drug designation.

Key Takeaways

This direct final rule is one FDA effort to support some sponsors' incremental shift from animal testing to other forms of nonclinical testing, when appropriate. The FDA's replacement of "animal" with "nonclinical," along with other conforming terminology changes, aligns with deregulation under Executive Order 14192 and other initiatives encouraging NAMs in place of animal testing in preclinical drug and biologic development.

Comments to the direct final rule must be submitted by December 7, 2026, and the rule will become effective February 4, 2027. We will continue to monitor developments in the transition from animal-based preclinical and nonclinical research to NAMs.

This blog was drafted by Brian Malkin, co-lead of the Spencer Fane FDA Pharmaceutical and Biologics Market Team. For more information, visit spencerfane.com.

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