information as of January 3. … The available information does not change the risk-benefit assessment for this review."

People with Alzheimer's disease aren't routinely tested for *APOE4* because it hasn't so far guided diagnosis and treatment. Although some scientists had hoped FDA would rule against giving lecanemab to people with two copies of *APOE4*, the agency instead suggested people "consider testing" for *APOE4* status "to inform the risk of developing ARIA when deciding to initiate treatment." Gandy's hospital expects to offer testing for *APOE4* to those interested in lecanemab, to help them better gauge their risk from the therapy.

The drug label approved by FDA also recommends that anyone taking lecanemab have three MRIs over roughly the first 6 months of treatment to watch for side effects, as well as an MRI before beginning treatment. Some scientists had hoped the agency would require that lecanemab be enrolled in FDA's Risk Evaluation and Mitigation Strategies (REMS) program for medications with "serious safety concerns." REMS can require that physicians prescribing a new drug report side effects to FDA, that the drug be administered in qualified health care settings, and that doctors get training about which patients may be at highest risk of dangerous side effects.

FDA did note that it's requesting "expedited reporting" of any deaths in ongoing trials and deaths from significant brain hemorrhages in people who take lecanemab postapproval. University of Cincinnati neurologist Alberto Espay also worries about recipients of the antibody who may develop less severe ARIA. For at least some of them, he says, "I cannot imagine it's irrelevant or inconsequential."

Discussion of these safety concerns comes amid continued debate over lecanemab's benefits. On an 18-point cognition scale, those getting the drug on average declined 0.45 points less than those getting placebo after 18 months. Neurologists disagree over whether patients and caregivers would perceive this difference. "It's really on the edge" of what's meaningful, says Lon Schneider, a geriatric psychiatrist at the University of Southern California Keck School of Medicine. The drug is "approvable, but like many medications that are approved it leaves much to be desired."

Others, such as Snider, say the benefits may well be noticeable. On the part of the scale that assesses orientation, she notes, an individual who scores 0.5 "can still drive" and get around independently. "If you go to a one, you're going to start getting lost."

The Alzheimer's Association, which has come out in favor of lecanemab, celebrated FDA's thumbs-up. And in the lead-up to the agency's decision, more than 200 researchers and physicians signed an open letter that endorsed the drug. Nearly half are recent consultants or grant recipients of Eisai or Biogen, *Science* has found.

Espay, however, argues FDA had painted itself into a corner with an earlier decision. He says officials "are victims of an artificially low bar" they set in 2021 when they approved another anti-amyloid antibody, aducanumab, even though FDA's advisory committee had voted against approval and the evidence that the drug worked was weak. (Last month, a congressional report described that approval process as "rife with irregularities.")

> **"Like many medications that are approved, it leaves much to be desired."**
>
> **Lon Schneider**, University of Southern California Keck School of Medicine

Both drugs were approved under FDA's accelerated approval pathway, which allows for decisions based on "surrogate endpoints," biological measures thought to predict clinical benefits to patients. In May 2022, Eisai had asked FDA to approve lecanemab based on evidence that it is highly effective at clearing the brain of amyloid plaques, the same surrogate endpoint cited in the aducanumab approval.

Many of the same FDA officials reviewed both drugs, and in both cases, the lead biostatistician, Tristan Massie, expressed hesitations. In the summary report for lecanemab, Massie questioned whether the surrogate endpoint "is reasonably likely to predict change on the clinical outcome." His colleagues didn't agree. "The Division notes the issues that Dr. Massie has raised but, overall, the findings" on amyloid plaques "appear robust and persuasive," they wrote.

But it's unclear whether the Centers for Medicare & Medicaid Services (CMS), the federal agency that pays for many treatments for older Americans, will reimburse for lecanemab. In April 2022, CMS announced it would decline to reimburse for aducanumab, except in certain clinical trials, tanking its commercial prospects. CMS also said it would only consider covering such anti-amyloid antibodies after full FDA approval.

In a statement after FDA approved lecanemab, the Alzheimer's Association called that stance "harmful and unfair" and called on CMS to reverse its position. ■

With reporting by Charles Piller, whose work was supported by the *Science* Fund for Investigative Journalism.

ANIMAL RESEARCH

# FDA no longer has to require animal testing for new drugs

## Agency can rely on animal-free alternatives before human trials

*By* **Meredith Wadman**

New medicines need not be tested in animals to receive U.S. Food and Drug Administration (FDA) approval, according to legislation signed by President Joe Biden in late December 2022. The change—long sought by animal welfare organizations—could signal a major shift away from animal use after more than 80 years of drug safety regulation.

"This is huge," says Tamara Drake, director of research and regulatory policy at the Center for a Humane Economy, a nonprofit animal welfare organization and key driver of the legislation. "It's a win for industry. It's a win for patients in need of cures."

In place of the 1938 stipulation that potential drugs be tested for safety and efficacy in animals, the law allows FDA to promote a drug or biologic—a larger molecule such as an antibody—to human trials after either animal or nonanimal tests. Drake's group and the nonprofit Animal Wellness Action, among others that pushed for changes, argue that in clearing drugs for human trials the agency should rely more heavily on computer modeling, "organ chips," and other nonanimal methods that have been developed over the past 10 to 15 years.

But pro-research groups are downplaying the law, saying it signals a slow turning of the tide—not a tsunami that will remake the drug approval process overnight. Jim Newman, communications director at Americans for Medical Progress, which advocates for animal research, argues nonanimal technologies are still "in their infancy" and won't be able to replace animal models for "many, many years." FDA still retains tremendous discretion to require animal tests, he notes, and he doesn't expect the agency to change tack anytime soon.

In order for a drug to be approved in the United States, FDA typically requires toxicity tests on one rodent species such as a mouse or rat and one nonrodent species such as a monkey or dog. Companies use tens of thousands of animals for such tests each year. Yet more than nine in 10 drugs that enter human clinical trials fail because they are unsafe or ineffective, providing grist to those who argue that animal experiments are a waste of time, money, and lives.

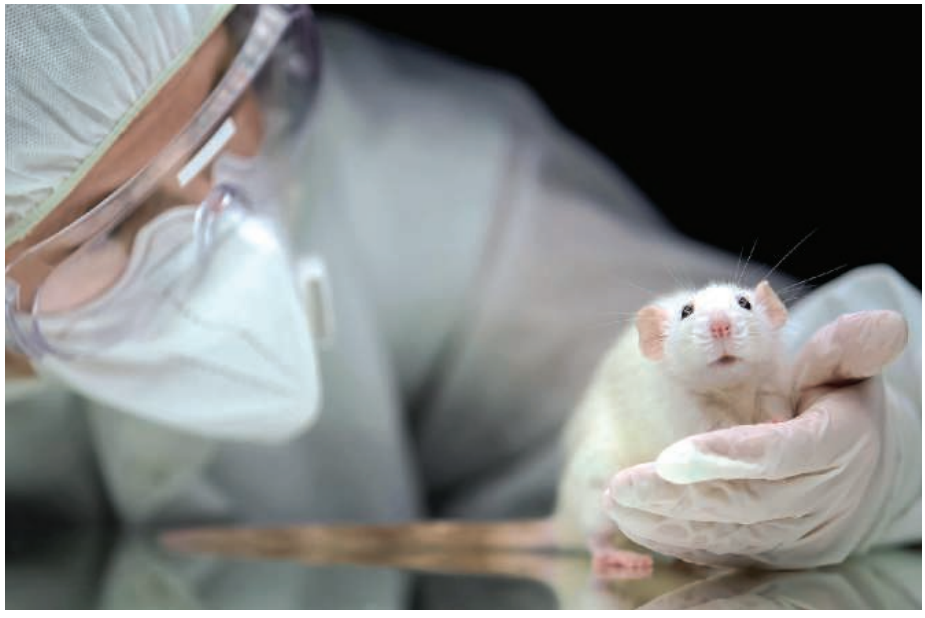
"Animal models are wrong more often than they are right," says Don Ingber, a Harvard University bioengineer whose lab developed organ chip technology now being commercialized by the company Emulate, where he sits on the board and owns stock.

Such chips typically consist of hollow channels embedded in silicone-based polymers about the size of a computer thumb drive. The channels are lined with living cells and tissues from organs such as the brain, liver, lung, and kidney. Fluids flow through them to mimic blood flowing through tiny vessels and fluid tracking through tissues, as it does in living organs. In the body, drug damage often shows up in the liver because it breaks down drugs for excretion. A human liver chip can warn of such toxicity when an experimental drug pumped through it damages the cells.

Last month, Lorna Ewart, chief scientific officer at Emulate, Ingber, and colleagues published a study highlighting the potential of this technology. The company's liver chips correctly identified 87% of a variety of drugs that were moved into humans after animal studies, but then either failed in clinical trials because they were toxic to the liver or were approved for market but then withdrawn or scaled back because of liver damage. The chips didn't falsely flag any nontoxic drugs.

Other animal alternatives include organoids—hollow, 3D clusters of cells that are derived from stem cells and mimic specific tissues. They have shown promise in predicting liver and cardiac toxicities. Proponents also tout the potential of digital artificial neural networks for rapidly identifying the toxic effects of drugs.

Some drug companies have chafed at FDA's animal testing requirement, arguing that animal studies cost them millions of dollars, slowing drug development and making the medicines that do reach the market far more expensive. In 2019, Vanda Pharmaceuticals sued the agency, charging that its requirement of additional toxicity testing of an antinausea drug in dogs was unreasonable. A U.S. judge ruled against the company in 2020, citing the animal testing requirement in what was then the law governing FDA's drug assessments.



Tens of thousands of rodents are used by companies for drug toxicity testing each year.

A liver chip made by Emulate contains cells and fluids found in the human liver.

Now, that requirement is gone. In eliminating it, Congress seems to have responded to the emergence of nonanimal methods and growing public sentiment against animal research. Senator Rand Paul (R–KY) and Senator Cory Booker (D–NJ), who both call animal research inefficient and inhumane, introduced the changes, which the Senate passed by unanimous consent in September 2022. In December, Biden signed them into law as part of the Consolidated Appropriations Act, which funds the government through this fiscal year.

Wendy Jarrett, CEO of Understanding Animal Research, an animal research advocacy group based in the United Kingdom, doesn't share animal advocates' delight at the changes. She says nonanimal methods can't capture all the ways a drug might put human trial participants at risk. "We can drop a new [candidate drug] onto a bunch of liver cells. And we can see that it doesn't damage them," she says. "But what we don't know is whether it's going to make the person cough, whether it's going to damage their intestines or their brain."

FDA's chief scientist says the agency is in favor of trying to move away from animal testing—when other approaches are ready. "We support alternative methods that are backed by science and provide the necessary data showing whether products are safe and effective," Namandjé Bumpus says. "We continue to encourage developers working on alternative methods to present their work to the FDA." She also notes that the agency requested and received $5 million this year to launch an FDA-wide program to develop methods to replace, reduce, and refine animal testing.

Still, it remains unclear just how much the new law will change things at FDA. Although the legislation *allows* the agency to clear a drug for human trials without animal testing, it doesn't *require* that it do so. What's more, FDA's toxicologists are famously conservative, preferring animal tests in part because they allow examination of a potential drug's toxic effects in every organ after the animal is euthanized.

The main impact of the new law is that it opens the way for FDA and a company to have a serious discussion about whether alternatives are adequate, says Steven Grossman, a former deputy assistant secretary of health who advises companies on their FDA applications. "It provides a little additional authority. It says in law: 'Congress is cool that these discussions are going on.'" ■



PHOTOS: (TOP TO BOTTOM) IEVGEN CHABANOV/ALAMY; EMULATE

# FDA no longer has to require animal testing for new drugs

Meredith Wadman

*Science*, **379** (6628), .
DOI: 10.1126/science.adg6276