Animal testing no longer required for drug approval, but high-tech substitutes aren't ready

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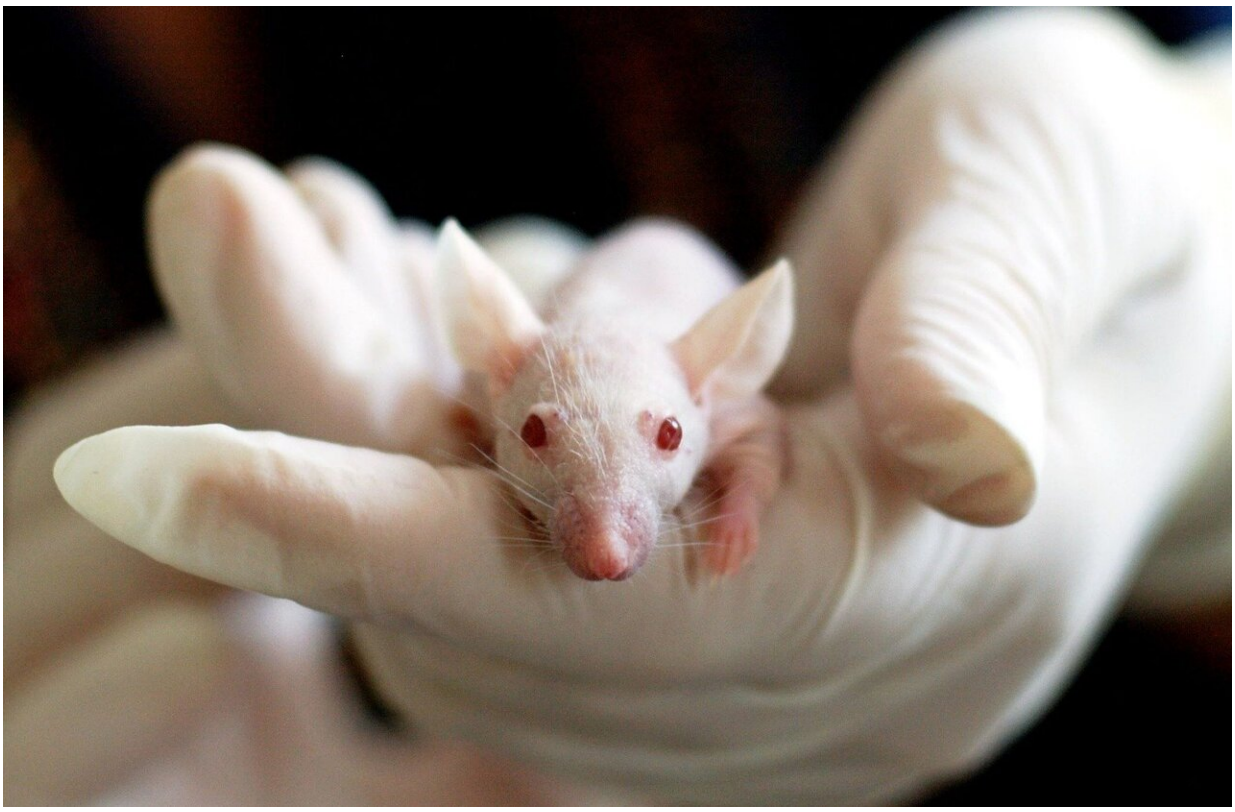

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For generations people have associated the terms "lab rat" and "guinea pig" with scientific research. Animal testing remains a standard and has

been required for drug approval.

Just before Christmas, though, Congress ended the requirement that all new drugs must be tested in two species—usually mice and a "higher order" mammal like rabbits or primates—before being tried in people.

The change won't stop animal testing overnight. Research tools and computer algorithms developed over the last 10 to 15 years still have gaps. And regulators won't immediately change their decades-long approach to proving safety and effectiveness.

But the law, officially called the FDA Modernization Act 2.0, marks a triumph in scientific research on human cells and technology and the culmination of 40 years of lobbying by animal rights activists.

"There's kind of a moment right now where the technology has developed enough and the awareness has also developed enough to make this possible," said Benjamin Freedman, a bioengineer at the University of Washington School of Medicine.

Animal studies help provide a measure of security that a drug could be effective and probably isn't extremely dangerous—but they're not foolproof. Roughly 90% of drugs that are shown safe and effective in animals turn out not to work as planned in people. Occasionally, drugs that seem safe in animal testing turn out not to be.

"The failure of the current system that relies on the use of animals for the first round of testing is an open secret," said Kathy Guillermo, senior vice president of the People for the Ethical Treatment of Animals, which has long fought against animal testing.

How will animals be phased out?

The Food and Drug Administration isn't going to allow drug makers to suddenly stop using animals in drug development, said Rachael Anatol, senior vice president of science and regulatory affairs for the Biotechnology Innovation Organization (BIO), a trade group.

Drug companies will have to show the FDA that they're not sacrificing safety or effectiveness by replacing animal testing, said Anatol, who recently left the regulatory agency.

"Getting the agencies comfortable and secure in this is going to be one bottleneck," she said.

The FDA did not respond to several requests for comment about the change.

The first drugs that are likely to see a difference are the "me too" products that are similar to those already on the market, she said.

Another early benefit from Congress' action is likely to come in the testing of botulinum toxin, which is used as Botox for medical and cosmetic treatment, said Danilo Tagle, director of the Office of Special Initiatives with the National Center for Advancing Translational Sciences, a division of the National Institutes of Health.

Botulinum toxin remains one of the deadliest known substances and can contaminate food. Every year, millions of mice are treated with a lethal dose of botulinum toxin to test the potency of each batch of the toxin, Tagle said.

Now, he's working with the Food and Drug Administration to replace those mice with cells in a dish. The replacement process won't happen for a year or two, and it won't lead to millions more mice in the world—the animals will simply not be bred for this purpose.

But substituting animals with a test on a lab plate will save time and money, pose less risk for lab workers and avoid the need to dispose of the contaminated animals, he said.

The tools that are replacing lab animals

Technology is "not there yet" to fully replace animal testing, Anatol said. But researchers can now take skin or blood cells from a patient with the disease of interest, grow the cells in a lab, and rapidly test hundreds of drugs to see if any can reverse whatever is going wrong.

Scientists are also developing "organoids"—mixing cell types from a particular organ, like the kidney, to mimic how a disease and drugs might affect it.

A similar technology called "organs on a chip" allows researchers to better represent the environment inside the body by mimicking the flow of blood past these organoids.

Freedman grows mini-models of kidney and lung disease.

"They are not organs but they have features that resemble tissues," said Freedman, whose latest study was published Dec. 23. The mini organs can show symptoms of disease, can be used to see if drugs reverse those symptoms, and investigate the effects at the cellular level, which would be difficult to do in an animal, he said.

Researchers are starting to link up these simulated organs—suggesting what might happen if a drug were swallowed, digested, entered the bloodstream and ended up in the liver, Freedman said.

But for the moment, these cellular models are still add-ons, not substitutes, for animal models.

"There's a little bit of a distance between what happens in the dish and what's going to happen if you were to put a medication or treatment into a body," Freedman said. "That's still something that needs to be worked out."

Moving away from animal models will be particularly helpful for rare diseases, where it may be expensive or nearly impossible to develop an animal model, and where the small number of patients may make it hard to justify such work, Tagle and Freedman said.

Using cells from patients instead could shave a year or two off the drug development process.

Artificial intelligence, machine learning and computer simulations are also getting more realistic over time, the experts at BIO said.

Biotechnology companies, particularly larger ones with more money to spend on research and development, are investing in artificial intelligence and machine learning technologies, hoping they will prove cost-effective in the long run, said Nick Shipley, BIO's chief advocacy officer.

"It has a lot of promise, that's why companies keep investing in it, but it hasn't quite gotten there yet," he said.

Why is this happening now?

The move away from animal testing is also being driven by cost.

In addition to the ethical issues of testing on primates, pandemic shut-downs—especially in China—made it harder and more expensive to obtain research monkeys in recent years, Shipley said.

"It is a matter of everyone's desire for moral, ethical reasons as well as financial reasons to get this shifted away from animal testing," he said.

Every primate now costs between $4,000 and $5,000 to buy, not including costs of housing and feeding, added John Murphy, BIO's chief policy officer. "It's a pain point," he said.

A 2019 survey of pharmaceutical experts predicted replacing animals could save between 10% and 26% of drug development research costs, though Murphy and Shipley doubted the savings would be that high.

Culture shift

Scientists have been trained to turn to animals when researching diseases that affect people.

"The first thing I'd think is 'what's the animal model I have to use?'" said Paula Cannon, a virologist at the Keck School of Medicine of the University of Southern California who studies HIV and COVID-19. Rhesus macaques are typically used in HIV research because their experience is similar to the human one.

But awareness is increasing among scientists, as well as the FDA and companies, that animal models have scientific limitations as well as ethical ones, she said.

"In the past there was a lot of box-checking. The FDA needs us to do this in 500 mice, so let's just do it," she said. "Now people are saying, is this the right model? Is this actually going to tell us anything?"

Although researchers try to minimize the harm they pose to animals, they recognize that there's an ethical cost to their studies, said Richard Born, a neurobiologist who teaches a class at Harvard Medical School on

social issues in biology, including the ethics of animal testing.

He asks students to consider whether animals should be used for research and whether federal tax dollars should pay for that research. Born previously used primates in some of his studies of the visual system.

The shift away from animals will also require movement on the part of both drug makers and regulators, the BIO executives said.

Companies will have to prove to the FDA that they have viable alternatives to animal testing, but they won't make that move until the FDA provides assurances that it will accept such alternatives, Shipley said.

"They're not going to throw stuff at the wall hoping the FDA likes it," he said. "They're going to want some signals from the FDA (first)."

The market will move to reduce or eliminate animal testing only when the FDA provides some incentive for it to, Murphy added.

"As long as people feel like FDA is going to continue to revert to what it's always done, I just don't think you'll see as much interest or investment as there should be."