FDA announces controversial ‘risk-based’ rules for CRISPR-edited animal technology

Novel biotechnology, like genome editing, holds tremendous potential to improve animal health, enhance farm productivity, improve nutrition, and even reduce the need for additional expensive medical animal interventions, such as the use of antimicrobials and vaccines. One example where biotechnology is being researched for use to benefit animal health includes the development of intentional genomic alterations in chickens to prevent the transmission of avian flu from wild birds.

Avian flu can kill thousands, or even millions, of infected birds in days. It also poses a danger to people who come into contact with infected animals. Genome editing may be able to halt animal-to-animal transmission of certain viruses or diseases by making efficient changes to an animal’s DNA that would ordinarily take years to complete through traditional breeding practices.

Intentional genomic alterations in animals can also directly help human health. We’ve already evaluated and approved several intentional genomic alterations in animals that produce drugs used to treat serious human diseases and illnesses. Other important uses of animals with intentional genomic alterations that address human health includes the production of better animal models to advance the study of new drugs that treat complex human diseases, like cancer or heart disease. These innovations can help researchers test promising new treatments in a setting that more closely reflects the etiology of human disease.

Organ and tissue transplants that are better suited for human implantation can also be derived from animals with intentional genomic alterations. This is another important way this technology can help address human health needs. These applications of genome editing hold promise to mitigate the enormous costs and mortality associated with late-stage organ failure. The FDA is committed to providing the resources needed to ensure all of these promising products and approaches are safe and effective, and help advance the agency’s public health mission.

For instance, over the past two years, we’ve hired scientists and dedicated existing staff with the appropriate expertise to form the Division of Animal Bioengineering and Cellular Therapies for the science- and risk-based evaluation of intentional genomic alterations in animals and animal cell, tissue, and cell- or tissue-based products. The aim of this division is to help efficiently advance beneficial technologies, and ensure that the resulting products are safe and effective. The Division includes expertise to support evaluation of complex scientific and technical issues related to molecular and cellular biology, epidemiology, genetics and genomics, bioinformatics, and biological chemistry.

The regulatory framework developed for intentional genomic alterations in animals is designed to be nimble in the face of rapidly advancing technology, while also providing clarity and predictability for researchers and developers on how the agency intends to regulate, or exercise discretion in enforcing, regulatory requirements, for intentional genomic alterations based on their inherent risks. Over the next year, the agency expects to release additional information through guidance, to provide more clarity about this risk-based framework.

[Editor's note: For a critical perspective on the FDA's proposals to regulate animal biotechnology, read: Viewpoint: FDA plan to regulate CRISPR-edited animals as drugs will keep innovative products off the market by Alison Van Eenennaam.]

Many developers have already engaged with the FDA on this framework. The agency continues to encourage companies, including small companies and individual investigators, to meet with the FDA's Center for Veterinary Medicine early in the development process to discuss proposed products and how regulatory requirements can be tailored to risk, ensuring safe, efficient development.

FDA regulation of intentional genomic alterations in animals includes an evaluation of safety and effectiveness, with a particular focus on animal and food safety, and is based on risk. As part of the FDA's risk-based approach, for intentional genomic alterationsin animals that pose minimal risk, we generally do not intend to enforce investigational and approval requirements. For example, the FDA intends to exercise enforcement discretion for intentional genomic alterations in laboratory animals that are used for research purposes and are not from food-producing species. For these intentional genomic alterations, the FDA does not expect developers to submit data to the agency prior to marketing. For some intentional genomic alterations in animals found to pose minimal risk, depending on the specific risks posed, the FDA will review data prior to deciding whether to exercise enforcement discretion. An example of this is animal models of human disease from food-producing species that are contained in controlled conditions and are never intended to enter the food supply.

For intentional genomic alterations that do go through the approval process, the FDA ensures that the intentional genomic alterations we approve are safe to the animal, and safe to anyone that eats food derived from the animal if it's a food-producing animal. We also need to take steps to ensure that the genomic alteration does what it's intended to do, i.e., the product is safe and effective.

The FDA will evaluate the safety and effectiveness of an intentional genomic alteration based on the

totality of the evidence presented, not from any one particular assessment or result. Our aim is to closely tailor regulation to risk, to make sure the process is efficient. We want to help beneficial new innovations advance to consumers. For example, for some intentional genomic alterations in animals, we may require data to demonstrate that the intended alteration is present and that no unintended alterations were made in the genome. Whole genome sequencing is one method that can be used to demonstrate this, however, it is not a requirement. Also, just because an unintended alteration may be present, it doesn't necessarily correlate with a safety concern.

The FDA has approved intentional genomic alterations in animals that provide a benefit to human health, including in chickens that produce a drug in their eggs used to treat patients with a rare lysosomal acid lipase deficiency and a drug produced in goat milk designed to treat a rare blood clotting disorder. Many other sponsors are working with the FDA to discuss products under development.

It's important to clarify that the FDA is not regulating an animal as a drug. Rather, the agency regulates the intentional genomic alteration in the animal, not the animal itself. We don't consider farmers or producers who simply purchase and raise animals with intentional genomic alternations to be drug manufacturers or their farms to be drug-manufacturing sites in the traditional sense of those terms. And we won't use nomenclature that could wrongly imply that the animals or the farms should be classified that way. Similarly, performing post-market surveillance is generally a requirement for sponsors of approved applications, not an obligation for farmers or producers.

In advancing our framework, we'll be mindful of concerns raised by some that the animals not be labeled as drugs, nor farmers face any new drug requirements simply because they have and raise these animals on their farms. We understand that the way we apply nomenclature in these settings could have adverse effects, potentially discouraging the adoption of otherwise beneficial new innovations.

And because these are novel technologies, the FDA's risk-based regulatory framework will continue to evolve as science and technology evolves. For instance, as the agency gains a better understanding of the potential risks associated with intentional genomic alterations in animals produced using novel technologies like genome editing — and as the fidelity and specificity of these tools continue to improve — we can expect regulations and data submissions will continue to become more streamlined and focused on assessing any residual uncertainties.

The Veterinary Innovation Program

As part of the Action Plan, the FDA's Center for Veterinary Medicine's Veterinary Innovation Program is well underway in advancing this new framework. Seven sponsors have already been accepted into the program. An additional 12 sponsors are in process and are expected to join the program within the next year.

cow

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Image: University of California – Davis

The Veterinary Innovation Program is for certain intentional genomic alterations in animals and animal cell, tissue, and cell- or tissue-based products seeking FDA approval. The goal of the Veterinary Innovation Program is to facilitate advancements in the development of innovative products for animals by providing greater certainty in the regulatory process, encouraging development and research in cross-cutting scientific domains, and supporting an efficient and predictable pathway to approval for safe and effective products including intentional genomic alterations in animals.

The Veterinary Innovation Program offers benefits including the opportunity for extensive interactions between sponsors and the FDA's Center for Veterinary Medicine. These interactions can increase the predictability of the regulatory pathway, enable a lower number of review cycles, and reduce the overall time to approval.

We believe by engaging with the FDA's Center for Veterinary Medicine throughout the approval process, sponsors maximize the ability to address potential challenges in product development and leverage data from multiple sources. They minimize the number of studies conducted to support approval, improve the efficiency of review, and maintain an understanding of current scientific and regulatory advancements.

An Innovative Future for Patients and Consumers

The existence and content of applications we receive is generally confidential. But there have been numerous publications about promising uses of technologies such as genome editing to make intentional genomic alterations in animals. This includes the development of pigs with an intentional genomic alteration to make them resistant to Porcine Reproductive and Respiratory Syndrome Virus. These alterations can reduce a significant source of animal reproductive failure, stunted growth, and animal suffering. In addition to impairing animal health, infected animals cost U.S. and European producers billions of dollars annually.

Researchers are also developing an intentional genomic alteration in cattle for [combating] Bovine Respiratory Disease, which produces a potentially life-threatening toxin in the lungs of affected animals. For U.S. cattle ranchers, this disease is the leading cause of early mortality. It produces major losses in animal growth, health, and quality. These are just some of the promising applications of this technology. There are numerous other examples of promising uses of intentional genomic alterations in animals under development that provide a benefit to public health. Some of these include the development of intentional

genomic alterations in animals as a source of organs and tissues for humans (xenotransplantation), the development of novel human drugs in altered animals with reduced human allergenicity, and reduction in the transmission of zoonotic diseases.

Committed to Fostering Innovations in Animal Biotechnology

On April 25, 2019, the FDA's Center for Veterinary Medicine, along with representatives from the FDA's Center for Biologics Evaluation and Research, will host a live-cast webinar to discuss policy changes to make the FDA's approach more flexible and risk-based. We'll also discuss current scientific evidence and regulatory science questions important for the FDA's decision-making for genome editing in animals.

The FDA has decades of experience facilitating the development of complex and innovative technologies, including plant biotechnology and human biologics, and has emerged as a trusted global regulator. The agency is also committed to taking steps to ensure confidence in approved products, including educating consumers about the safety and benefits of the products of biotechnology. We are developing agricultural biotechnology consumer education initiatives, in partnership with USDA and EPA. Those initiatives should launch this year.

Scott Gottlieb, M.D., is the outgoing Commissioner of the FDA. Anna Abram is the FDA's Deputy Commissioner for Policy, Legislation and International Affairs.

Read full, original article: FDA Advancing Beneficial Animal Biotechnology Product Development