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Regulatory Pathways Emerge For Gene-Edited Products

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There has long been uncertainty about when and how regulators would respond to emerging genetic technologies such as gene editing, as the current U.S. regulatory system was not designed to address these technologies. Under the current system, it is unclear whether products developed through the use of these new technologies fall within the scope of regulation and what factors, if any, should be considered to assess risk. This ambiguity has raised issues for a range of innovators who are quickly adopting gene editing techniques — including CRISPR (the clustered regulatory interspersed short palindromic repeats), ZFN (zinc finger nucleases), TALENs (transcription activator-like effector nucleases), and RNAi (RNA interference) — as more targeted, efficient tools to achieve desired products.


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At long last, in a series of recent publications, the three agencies responsible for the Coordinated Framework for Biotechnology, namely the U.S. Department of Agriculture, Food and Drug Administration and the Environmental Protection Agency have finally provided some indication of how they view these novel techniques. While the agencies' respective proposals are early-stage and incomplete, their importance should not be underestimated. The proposals lay the groundwork for what could ultimately be applicable to a coming "profusion" of novel products of biotechnology, as anticipated in a recent report by the National Academy of Sciences.[1]

In our view, the regulatory proposals are mixed and somewhat inconsistent between agencies. While some would reduce regulatory burdens for gene editing (and other genetic technologies) based on risk, others have the potential to impose significant burdens simply based on the use of gene editing without being tied to risk. These proposals came out in January 2017, before the change of administration, making it is unclear whether and how the new administration will follow through. Importantly, the regulatory agencies invite comment on their proposals, as well as issues related to assessing risk. It is important for stakeholders to take this opportunity to shape policy in a rapidly evolving area.

Coordinated Framework Agencies Consider Regulation of Gene Editing

The FDA, USDA, and EPA have all indicated that they intend to make changes to their regulation of biotechnology products to address gene editing. However, their approaches differ. The FDA's Center for Veterinary Medicine has taken the most expansive approach by proposing to regulate all animals modified through gene editing. Specifically, CVM proposes to amend its existing guidance on the regulation of genetically engineered (GE) animals to specify that animals that are "intentionally altered"

through gene editing are subject to premarket review under the FDA's new animal drug authorities.[2] This means that gene-edited animals, such as dairy cattle that have been modified to produce hornless cows or pigs that have been modified to be resistant to viruses, could be subject to FDA's rigorous and often protracted premarket review process for new animal drugs. While CVM requests input on whether there may be data demonstrating that certain types of genome editing may pose minimal risk,[3] it has avoided proposing a risk-based paradigm for regulation. Instead, CVM retains a list of factors it would consider in determining whether to exercise "enforcement discretion" over a GE animal, such as whether the product is regulated by another agency or whether the product is contained in a certain manner. These factors, however, are not premised on the level of risk associated with the underlying genetic modification itself. The proposal thus risks being overbroad in the context of the coordinated framework's risk-based mandate, which directs agencies to establish frameworks based on the risks of the product and not the process by which the product was developed. Comments on CVM's proposal are due by April 19, 2017.

The FDA's Center for Food Safety and Applied Nutrition is taking a more interactive approach, based on its longstanding "consultation" program for evaluating the safety and regulatory status of food from GE plants. Thus, instead of taking a position, CFSAN and its counterpart for animal foods within CVM, have asked for stakeholder input on the appropriate approach to gene editing. More specifically the CFSAN and CVM request comment on the use of gene editing techniques to produce plant varieties used for human or animal food to help the agency assess whether there are food safety risks that should be considered and whether there are categories of products that may pose less risk than others.[4] The comment period for the request is scheduled to close on April 19, 2017.

In a manner simultaneously expansive and limiting, the USDA's Animal and Plant Health Inspection Service has also proposed changes to its regulatory regime to address gene editing. APHIS published a proposed rule that would update its regulation of GE organisms (under 7 C.F.R. Part 340), to include gene-edited organisms within the scope of regulation.[5] At the same time, APHIS proposes to streamline its approach to proactively exclude certain gene-edited organisms, as well as other GE organisms, from regulation based on its assessment of risk. In this sense, APHIS' changes, if finalized, could significantly reduce regulatory hurdles for companies developing and bringing gene-edited products to market.

The nuances of APHIS' proposal are important. Organisms modified solely by genetic deletions that could otherwise be obtained through chemical- or radiation-based mutagenesis would not be subject to USDA review, unless they posed a plant pest risk. Similarly, "null segregants," (where the offspring of a GE organism do not contain the genetic modification) would be exempt from regulation. APHIS' approach here is unsurprising — to some degree, the agency is simply proposing to codify risk-based principles it has developed in exempting specific gene-edited plants from regulation, including a line of waxy corn[6] and a white button mushroom[7] developed by CRISPR technology. The comment period for the APHIS proposed rule closes June 19, 2017.

The EPA has not articulated a clear position regarding its regulation of gene-edited products. The EPA's Office of Pesticide Programs has stated only that it intends to clarify its approach to pesticidal products derived from gene editing techniques in a manner that is consistent with the policies set forth in the coordinated framework.[8] This statement suggests that EPA will regulate the products of gene editing based on environmental risks that are reasonably posed by such products.

APHIS Takes a Step Toward Greater Risk-Based Regulation of GE Organisms

In addition to addressing gene editing, it is also worth noting that APHIS has proposed a wholesale shift in its regulatory approach to GE organisms that could meaningfully reduce regulatory burden for a range of novel organisms based on risk. The proposed changes would shift the current regulatory process from a "regulate first/analyze later" system, which presumes regulation based on the use of genetic material from a plant pest in the development of a GE organism, towards a process by which the risks of the GE organism are assessed before imposing permit and control requirements.

Under the proposed changes, APHIS would not require a permit or controls for movement or environmental release of a GE organism, as currently required, if it determines that the organism in question does not pose a plant pest risk. If APHIS concludes that the GE organism does pose a risk, any permit or other control, would be commensurate with that risk. This approach is arguably consistent with the coordinated framework's risk-based approach and in APHIS' view would result in fewer organisms ultimately subject to regulatory requirements[9]; however, it could be impractical because companies would need to wait for APHIS assessment prior to moving forward with development programs and, as anticipated by the NAS report, APHIS could quickly become overwhelmed.

Conclusion

The FDA, USDA and EPA have finally given some insight as to how they intend to regulate the products of gene editing. Their respective proposals differ in scope and approach; each proposal, however, has the potential to significantly shape how gene editing is integrated into product development. It is important for stakeholders to understand these developments and to engage with regulators as gene editing and other technologies continue to evolve.

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[2] FDA, Draft Guidance for Industry, Regulation of Intentionally Altered Genomic DNA in Animals (Jan. 2017), https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/Guidancef

orIndustry/UCM113903.pdf.

[3] FDA, Notice of Availability, Draft Guidance for Industry, Regulation of Intentionally Altered Genomic DNA in Animals, 82 Fed. Reg. 6561 (Jan. 19, 2017), available at: https://www.federalregister.gov/documents/2017/01/19/2017-00839/regulation-of-intentionally-altered-genomic-dna-in-animals-draft-guidance-for-industry-availability.

[4] FDA, Request for Comments, Genome Editing in New Plant Varieties Used for Foods, 82 Fed. Reg. 6564 (Jan. 19, 2017), available at: https://www.federalregister.gov/documents/2017/01/19/2017-00840/genome-editing-in-new-plant-varieties-used-for-foods-request-for-comments.

[5] USDA, Proposed Rule, Importation, Interstate Movement, and Environmental Release of Certain Genetically Engineered Organisms, 82 Fed. Reg. 7008 (Jan. 19, 2017), available at: https://www.regulations.gov/docket?D=APHIS-2015-0057.

[6] Letter from USDA/APHIS to DuPont Pioneer, Confirmation of Regulatory Status of Waxy Corn Developed by CRISPR-Cas Technology (Apr. 18, 2016), available at: https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-352-01_air_response_signed.pdf.

[7] Letter from USDA/APHIS to Pennsylvania State University, Request for Confirmation that Transgene-Free, CRISPR-Edited Mushroom is not a Regulated Article (Apr. 13, 2016), available at: https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-321-01_air_response_signed.pdf.

[8] Executive Office of the President, National Strategy for Modernizing the Regulatory System for Biotechnology Products, 17 (Sept. 2016), available at: https://www.epa.gov/sites/production/files/2016-12/documents/biotech_national_strategy_final.pdf.

[9] USDA/APHIS, Questions & Answers: APHIS Requests Public Input on Next Steps Towards Revision of its Biotechnology Regulations (Jan. 2017), available at: https://www.aphis.usda.gov/biotechnology/downloads/340/q&a_biotech-reg-revisions.pdf.
