Science & Technology Policy Topic: USA Genome Editing of Pigs Backgrounder
Word Count: 1200

To: Senator Patty Murray, Chair of the U.S. Senate Committee on Health, Education, Labor & Pensions (HELP)

From: Science and Technology Policy Analyst

Date: March 20, 2022

Subject: USA Genome Editing of Pigs

Executive Summary

Gene-editing technology has been constantly used in medical treatment development. Pigs are a spotlight among gene-edited products because of its close relationship with human and its multi-functions. With newer, more precise, and more efficient techniques of gene-editing, the U.S. FDA now considers gene-edited products being different from gene-modified ones, but continues to collect public comment and amends regulations accordingly.

Historical Background

Gene-editing is a technology in advanced molecular biology techniques that facilitates precise, efficient, and targeted modifications at genomic loci.[i] It enables us to alter the gene expression patterns in a pre-determined region to develop improved crop or food varieties by transforming valuable traits or removing undesirable traits in contemporary agriculture.[ii] The technique has been applied to medical research such as developing new treatments, vaccines, and drug therapies, entertainment and commercial activities such as Glo-fish pet that glows, and is recently expected to benefit the globe facing challenges from the high density of population, which is projected to exceed 9 billion by 2050, and the need to improve food quality with fewer inputs. The primary value of this technology is the shorter time needed, the easier design process, and the higher possibility of satisfied outcome than traditional grafted crops.

Regulations about gene-edited foods or drugs have followed the flow of technique improvements and product inventions, and extended issues of safety and ethics since early 2000s. In 2001, the first gene-targeted anticancer therapy drug, Glivec (imatinib), was approved by the U.S. FDA. Later in 2006, Gardasil was the first preventive cancer vaccine to gain the approval from FDA and to reach the market.[iii] For decades since 1985, zinc-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) has been applied to genome editing techniques. The development of clustered regularly interspaced short palindromic repeats (CRISPR) with CRISPR associated nucleases (Cas) is claimed to provide a simpler way to edit genome patterns and recovered in the year of 2012. By making precise targeted cuts in DNA, CRISPR ushered in endless potential in areas of medicine, agriculture, biomaterials, etc.[iv] However, CRISPR-Cas9 gene-editing technology also draws many controversies about the safety and steadiness because the longer CRISPR stays active in cells, the more likely it is to edit off-

target parts of the genome and potentially causes dangerous side effects.[v] Among the multiple gene-edited crops or foods, pigs face extreme controversy because it is very close to human beings and has functions than becoming dishes.

Pigs serve as an important agricultural resource and animal model in biomedical studies. Applications of gene-editing technology on pigs can confer desired phenotypes to pigs to improve production traits, such as optimal meat production, enhanced feed digestibility, and disease resistance. Besides, given their genetic, anatomic, and physiologic similarities to humans, pigs can also be modified to model human diseases or to serve as an organ source for xenotransplantation to save human lives. Although the techniques for organ transplantation from pigs to human still need further research to avoid severe immune rejection in human bodies, many genetically modified pig models with agricultural or biomedical values have been established by using gene editing tools. These pig models are expected to accelerate research progress in related fields and benefit humans.[vi]

Current Gene-edited Pigs Standards

USDA has clearly stated that gene editing is not GMO, and that gene-editing products are not part of the same regulatory oversite as GMOs are in the U.S. The fact that it is nearly impossible to detect whether an organism's DNA has been edited or not because the changes are indistinguishable from naturally occurring mutations is a key point for the decision. In addition, the U.S.-Mexico-Canada Agreement (USMCA) that was signed into law in early 2020 reportedly includes provisions to support gene editing. While this distinction is under debates, it is clear that gene-editing offers a research tool to help discover how genes work and is not yet banned or strictly regulated. [vii]

In January 2017, the U.S. FDA released draft revised Guidance for Industry (GFI) #187, "Regulation of Intentionally Altered Genomic DNA in Animals," and requested public comment regarding the regulation of intentionally altered genomic (IGAs) DNA in animals, including animals produced through the use of genome editing technologies and genetic engineering (GE).[viii] FDA generally regulates the IGAs that are introduced into the animals' genomes as new animal drugs and approvals are given to products that are effective to meet what the developers claim to reach and are safe for anyone that may consume food from the animal.[ix] While animals with IGAs themselves are not regarded as drugs, both the U.S. and Canada have decided that there is no need to regulate genome editing technology specifically and additionally if it is possible through traditional means, meaning that genome-edited crops are not subject to genome-modified crop safety protocols and labeling requirements.[x] FDA wishes to exercise enforcement discretion to sponsors producing an IGA product in animal when the risks is determined to be low. However, the draft revised guidance regulates the assessing dimensions of the degree of the

potential environmental impacts in addition to safety concerns for IGAs in animals for developers in approval applications. The developers should submit descriptions including a broad statement characterizing the product of the animal, the steadiness of the method and effects of the IGA, the way of passing the IGA to its offspring, the characteristics of the resulting animal and its health, the impacts to environment, ecosystem, and food safety, and the validity of developer's claim to seek FDA's approval to reach the market.

Stakeholder Values

To date, there are still few gene-editing products in the market. The latest one is a GABA-fortified tomato developed using CRISPR-Cas9 technology being launched in Japan in September 2021. But this will not be the end of gene-edited crops and foods. The scientists continue to develop more desirable crops and foods with gene-editing technology.

Clinical Therapy Development

Gene-editing techniques are critical in medical treatment and therapy development. Research relative to human gene-editing are banned by the National Institutes of Health and the National Science Foundation, but those not implementing on human beings are allowed. While pigs are involved for possible organ transplantation to human, and many more treatments expected to prevent or cure diseases are beneficial, biomedical researchers mainly support the allowance of innovations of IGAs in animals to improve humans' quality of lives.

Agriculture and Food Supplement

Food industry mostly opposes to more and stricter regulations regarding gene-edited food development and patent application approvals. In addition to the benefits of IGAs in food supplying by increasing the production and producing products that better meet consumers' needs, large food companies are also allowed to accumulate more patents for their inventions with each new trait. Syngenta Group claimed that this new technology must be used to sustainably feed a growing global population.[xi] But the phenomenon has also alarmed many crop breeders and farmers' rights activists, who fear it will disrupt the global food market, crowd out small businesses and stifle innovation.

Food-safety and Environmental Concerns

To consumers and environmentalists, the potential and chronic threats of gene-editing technology to organisms, biodiversity, water and soil, and human health are most worried for. [xii]Current studies are lack of evidence proving that IGAs in animals are as stable and share equal effects as natural selection. Nonetheless, these techniques can also be applied to allergy avoiding,

benefiting groups of people without constraints to food choices due to one allergic person in the group, such as the lunch at school.

[xiii] [xiv] [xv] [xvi] [xvii] [xviii] [xix]

---

[i] Zhang, Y., Massel, K., Godwin, I.D. *et al.* (Nov. 30, 2018.) Applications and potential of genome editing in crop improvement. *Genome Biol* **19,** 210 (2018). https://doi.org/10.1186/s13059-018-1586-y.

[ii] Abdallah NA, Prakash CS, McHughen AG. Genome editing for crop improvement: Challenges and opportunities. *GM Crops Food.* **6(4):**183-205 (2015). doi: 10.1080/21645698.2015.1129937.

[iii] History of genetic engineering and the rise of genome editing tools. Synthego. Retrieved on Apr. 20, 2022 from https://www.synthego.com/learn/genome-engineering-history.

[iv] Ibid.

[v] Charles Choi. (June 7, 2021.) 抗 CRISPR 蛋白可幫助基因編輯「踩剎車」。Retrieved on Apr. 13, 2022 from https://cen.acs.org/biological-chemistry/gene-editing/cn-Anti-CRISPR-proteins-help-put/99/i21#:~:text=CRISPR%EF%BC%88%E6%88%90%E7%B0%87%E7%9A%84%E3%80%81%E8%A7%84%E5%BE%8B,%E5%BE%AE%E7%94%9F%E7%89%A9%E9%98%B2%E5%BE%A1%E7%B3%BB%E7%BB%9F%E7%9A%84%E4%B8%80%E9%83%A8%E5%88%86%E3%80%82.

[vi] Huaqiang Yang and Zhenfang Wu. (Sep. 4, 2018.) Genome Editing of Pigs for Agriculture and Biomedicine. *Frontiers in Genetics.* https://doi.org/10.3389/fgene.2018.00360. https://www.frontiersin.org/articles/10.3389/fgene.2018.00360/full.

[vii] Courtney Schmidt and Lon Swanson. Genetically modified vs. gene editing. Wells Fargo. Retrieved on Apr. 23, 2022 from https://global.wf.com/hub_article/genetically-modified-vs-gene-editing/.

[viii] U.S. Food & Drugs Administration. (Jan. 2017.) Guidance for Industry #187: Regulation of Intentionally Altered Genomic DNA in Animals.

[ix] Q&A on FDA Regulation of Intentional Genomic Alterations in Animals. U.S. Food & Drugs Administration. Retrieved on Mar. 23, 2022 from https://www.fda.gov/animal-veterinary/animals-intentional-genomic-alterations/qa-fda-regulation-intentional-genomic-alterations-animals.

[x] Jessica Davis Pluss. (Jan. 31, 2022.) Explainer: the controversy behind genome editing our food. SwissInfo.ch. Retrieved on Mar. 23, 2022 from https://www.swissinfo.ch/chi/%E5%9F%BA%E5%9B%A0%E7%BB%84%E7%BC%96%E8%BE%91%E9%A3%9F%E5%93%81%E8%83%8C%E5%90%8E%E7%9A%84%E4%BA%89%E8%AE%AE/47293390#:~:text=%E7%BE%8E%E5%9B%BD%E5%92%8C%E5%8A%A0%E6%8B%BF%E5%A4%A7%E5%9D%87%E5%86%B3%E5%AE%9A,%E5%8C%85%E5%90%AB%E4%BA%86%E5%A4%96%E6%BA%90DNA%E3%80%82.

[xi] Jessica Davis Pluss and Pauline Turuban. (Jan. 31, 2022.) Genome editing's patent problem fuels concern for the future of food. SwissInfo.ch. Retrieved on Mar. 23, 2022 from https://www.swissinfo.ch/chi/%E5%9F%BA%E5%9B%A0%E5%BA%8F%E5%88%97%E5%B0%88%E5%88%A9%E5%95%8F%E9%A1%8C%E5%BC%95%E7%99%BC%E5%B0%8D%E7%B3%A7%E9%A3%9F%E6%9C%AA%E4%BE%86%E7%9A%84%E9%9A%B1%E6%86%82/47307124.

[xii] Ibid.

[xiii] Sara Reardon. (Oct. 6, 2015.) Gene-editing record smashed in pigs. *Nature (2015)*. https://www.nature.com/articles/nature.2015.18525.

[xiv] Beate Rieblinger, Hicham Sid, Denise Duda, *et al.* (Mar. 3, 2021.) Cas9-expressing chickens and pigs as resources for genome editing in livestock. *PNAS* **118** (10) e2022562118. https://www.pnas.org/doi/10.1073/pnas.2022562118.

[xv] Gene editing could pave way for pig organ transplants-US study. Reuters. Retrieved on Apr. 16, 2022 from https://www.reuters.com/article/genome-editing-pigs/gene-editing-could-pave-way-for-pig-organ-transplants-us-study-idUSL1N12C0Z220151012.

[xvi] Antonio Regalado. (Dec. 11, 2020.) Gene editing has made pigs immune to a deadly epidemic. MIT Technology Review. Retrieved on Apr. 17, 2022 from https://www.technologyreview.com/2020/12/11/1013176/crispr-pigs-prrs-cd163-genus/.

[xvii] 基因編輯食品，是否能端上我們的餐桌？ jiemian.com. Retrieved on Apr. 16, 2022 from https://www.jiemian.com/article/5555163.html.

[xviii] Yihao Yang, Chenda Xu, Ziyan Shen, and Changjie Yan. (Jan. 31, 2022.) Crop Quality Improvement Through Genome Editing Strategy. *Frontiers Genome Ed.* **3:**819687. doi: 10.3389/fgeed.2021.819687.

[xix] Menz J, Modrzejewski D, Hartung F, Wilhelm R and Sprink T. (Oct. 9, 2020) Genome Edited Crops Touch the Market: A View on the Global Development and Regulatory Environment. *Front. Plant Sci.* **11:**586027. doi: 10.3389/fpls.2020.586027.