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before the

**Joint Subcommittees on Livestock and Foreign Agriculture and Biotechnology,
Horticulture, and Research**

RE: “Agricultural Biotechnology: 21st Century Advancements and Applications”

October 26, 2021

Introduction

Good morning Chairwoman Plaskett, Chairman Costa, Ranking Member Baird, Ranking Member Johnson, Congresswoman Kim Schrier from Washington State and members of the Subcommittees. My name is Jon Oatley and I am the Associate Dean of Research and a Professor in the College of Veterinary Medicine at Washington State University.

WSU is Washington State’s land-grant university and a public research university committed to its mission and tradition of service to society. With six campuses across the state of Washington and a presence in every county through its Extension system, WSU has an enrollment of 31,159 students statewide. In FY2020, WSU’s total research and development expenditures exceeded \$350 million. The College of Veterinary Medicine at WSU is a flagship program for the university that houses five departments with a cadre of stellar faculty and staff studying an array basic and applied life and health sciences topics.

My testimony today will reflect how I see the current state of biotechnology applications in animal agriculture, in particular the potential impact of gene editing technologies for improving how the human population is fed now and in the coming decades. The lens I see the animal biotechnology arena through has been shaped by an array of experiences. Beyond serving as a research administrator for a tier 1 land-grant university, I am a scientist and developer of gene editing applications in farm animals. In addition, I have gained an academician’s perspective on early-stage navigation of the federal regulatory approval process for biotechnology in animal agriculture through interaction with the Food and Drug Administration (FDA). I also worked with the American Association of Veterinary Medical Colleges (AAVMC) and Association of Public and Land-Grant Universities (APLU) to establish the recent task force on gene editing in livestock and subsequently served as a core member.

A genome is the complete set of genetic information contained within DNA that is present in a cell or organism. Genetic engineering can be defined simply as the manipulation of an organism’s genome by way of human intervention. With food animals (e.g. livestock such as cattle, pigs, chickens, sheep, etc.), humans have been engineering the genome for thousands of years via selective breeding as an effort to improve how protein products are generated. This ancient practice is still used today and impacts, both positive and negative, can be observed in all livestock sectors. While opportunity still exists for making gains in traits of livestock to feed the growing

global human population that is projected to reach nearly 10 billion by the year 2050, the pace and precision needed to ensure the future of food security is not achievable with this strategy alone. Application of cutting-edge technologies such as CRISPR gene editing offers a new frontier for tailoring the traits of livestock for optimized growth, resiliency, and climate smart performance in a variety of environments and within a timeframe of months to years rather than decades and generations that selective breeding requires.

Global adoption of innovation in production of agricultural animals can significantly strengthen the food supply and positively impact economic prosperity of the U.S. Applications of gene editing to enhance the traits of animals is the present and future of innovation in livestock production. For the promises of this groundbreaking technology to be realized in feeding the future, processes for federal regulatory approval and monitoring must be rooted in science and aligned to the pace of development. A modernization of the U.S. federal regulatory framework governing applications of genetic modification in animals, including gene editing, is needed for streamlined and cost-effective approval and monitoring. In doing so, the science of gene editing can be advanced from research laboratory to the public domain in a safe and effective manner never before seen in the U.S., thereby addressing the real-world challenges with food security now and over the next 100 years.

Background on Feeding the Human Population through Animal Products

The origins of animal genome engineering by humans are ancient, being traced to over 10,000 years ago following domestication of various species which led to the practice of selective breeding that is still in use today. The central purpose of this intervention has been to shape the traits of animals that generate products (e.g. meat, milk, and fiber) for human consumption. The demand for animal sourced protein in the human diet has always existed and continues to rise as more people are added to the planet every day. According to statistics from the United Nations Food and Agricultural Organization (FAO), the global demand for animal protein increased by ~80% between the years of 1970 and 2000; this trend is expected continue in lockstep with human population growth¹.

Food security is a critical global issue. The United Nations Population Division projects that there will be 9.8 billion people on earth by the year 2050. Providing food at sufficient quantity and nutritional quality for this number of people will require major improvements in production efficiency for both plant and animal agriculture so that outputs for human consumption are generated from minimal inputs and accomplished in a climate smart way.

The intrinsic element of both plants and food animals that significantly influences traits for resiliency and production of products for human consumption is the genetic makeup or genome. Although the conventional practice of selective breeding has had major impact on physical traits of food animals since the dawn of domestication, advances are often incremental and take decades to manifest. In addition, the lack of precision and need for multiple generations to achieve material gains through use of selective breeding carries an inherent risk of creating unintended negative genetic combinations that reduce the welfare, resilience, and production efficiency of a food animal. For these reasons, the common livestock production practice of selective breeding is not sufficient to meet the demands of food security that arise from an exponentially expanding human population.

¹ <https://www.fao.org/documents/card/en/c/cb4474en>

The future of food animal production must align to a goal of feeding more with less. As arable land and water resources continue to decline globally, production of animal sourced protein through livestock production will need to increase with use of fewer inputs. In addition, although agriculture accounts for only 10% of greenhouse gas emissions in the U.S.², livestock production is still considered a major contributor to global warming and climate change. The farm animal of the future will need to be resilient in ever changing and often harsher climates while contributing a reduced carbon footprint; farming practices and livestock will need to evolve to be climate smart.

The science of gene editing holds major potential to address global food security now and for the future. As a biotechnology, gene editing applications in animals are subject to approval and monitoring at the federal level. As gene editing strategies such as CRISPR technology are evolving to dramatically expand the toolbox for precision agriculture, so must the federal regulatory framework.

Overview of Biotechnology Approaches to Shape the Genome of Animals

The science of animal biotechnology has held great promise for decades as a modern-day complement to selective breeding for the shaping production traits of livestock. Indeed, the diverse field of biotechnology is regarded as a major component of the ongoing fourth industrial revolution. Although much of the animal side of the biotechnology sector is still in a research and development phase, the advent of gene editing technologies and their rapid deployment as tools in the animal research arena has led to several applications in livestock that are poised for entry into the marketplace.

A first generation of approach for genetic engineering of livestock is the science of transgenesis. This conventional biotechnology involves the use of recombinant DNA for integration of genetic information found in other organisms into a target animal's genome. As such, genetic changes made by way of transgenic technologies could not arise in nature and have resulted in livestock possessing them being labeled "genetically modified organisms" or GMOs.

Unlike conventional approaches to genetic engineering of animals such as transgenesis, gene editing technologies can precisely target specific sites in the genome to bring about favorable changes using natural processes within a cell or organism. Importantly, many gene editing applications do not involve integration of recombinant or foreign DNA into the genome of an animal. Rather, the gene edit is simply created by breaking DNA at a precise spot in the genome and relying on the repair of that break to bring about a change. This process of DNA breaking and being repaired in a different way is inherent to mammalian cells and occurs constantly in animals. Gene editing simply directs where a DNA break and natural repair change will happen.

Public attitudes to genetically modified organisms have tended to be negative. In the U.S., the 2019-2020 Pew Research Center's International Science survey reported that 27% of Americans thought GMOs were generally safe to eat, 38% responded they were unsafe to eat, and 33% said they did not know enough about the topic to say³. This negative perception of food derived from GMOs has presented a major impediment for advancing biotechnology applications to improve livestock production in the public domain.

² <https://www.epa.gov/ghgemissions/sources-greenhouse-gas-emissions>

³ <https://www.pewresearch.org/science/2020/12/10/biotechnology-research-viewed-with-caution-globally-but-most-support-gene-editing-for-babies-to-treat-disease/>

Currently, the leading edge of biotechnology application for genetic engineering of livestock has moved from the conventional and often time imprecise nature of transgenesis to precision approaches of gene editing. Importantly, the technical science and intended outcomes of gene editing in livestock are substantially different compared to transgenesis. Thus, a “one box fits all” model for regulatory statutes in the U.S. should not be applied to genetic engineering of livestock. A model that allows for fluidity to adapt with contextual categorizing of the genetically altered animals and applying logic-based decision making, while still ensuring safety, is needed.

In contrast to inherent randomness and dependence on the possibility of admixture of favorable versions of genes that conventional breeding is based on, gene editing offers a precise and efficient means for introducing favorable genetic elements into the genome of animals that will drive beneficial traits for improving the production of meat, milk, or fiber for human consumption. Applying gene editing to create lines of livestock with unique and enhanced genotypes is an efficient way to help ensure food security. To realize this potential, global regulations and policies must be framed to allow for facilitated deployment of the technology into production systems and the widespread dissemination of gene edited animals into the food chain, while still ensuring the safety of the food from these animals, as well as the welfare of the animals and the environment.

Leading Edge Applications of Gene Editing in Farm Animals

With the advent of gene editing technologies for mammalian cells nearly a decade ago, a new frontier was opened for the application of biotechnology to improve food animal production. Over the last 5 years, several applications of gene editing in livestock have been devised and advanced to the brink of being useful for U.S. farmers and ranchers. The leading edge of gene editing applications in production animal agriculture can be defined as improving growth efficiency, disease resistance, welfare, and reproductive capacity. Recent reports of gene edits in pigs that confer resistance to Porcine Reproduction and Respiratory Syndrome Virus^{4,5} and produce surrogate breeding strategies for a range of livestock⁶ and poultry⁷ to advance genetic gain are poised to make significant impacts on food animal production in the U.S. and globally. At present, none of these gene editing applications have fully navigated the U.S. federal regulatory approval process and are therefore unable to be capitalized on by America’s farmers and ranchers to enhance the food supply and economic prosperity of the agriculture sector.

Reproductive capacity is a staple of livestock production. The flow of genetic information between generations occurs through sperm and eggs. Thus, the basis of selective breeding that has been used for thousands of years to shape the traits of animals is directing the combination of sperm from choice males and eggs from choice females. Most genetic change in livestock production is made through selective use of males because millions of sperm are made every day for directed breeding purposes. This principle of selected use of breeding males has had enormous impacts on shaping what the world’s livestock populations look like today, but the impact was kept primarily on a regional scale until the 1950s when artificial insemination technology was developed. This breeding strategy allows for collecting of sperm from what are deemed elite or genetically desirable males and shipping around the world for artificial introduction into females that would result in pregnancies. Effective application of artificial insemination in livestock production

⁴ <https://pubmed.ncbi.nlm.nih.gov/29925651/>

⁵ <https://pubmed.ncbi.nlm.nih.gov/26641533/>

⁶ <https://pubmed.ncbi.nlm.nih.gov/32929012/>

⁷ <https://pubmed.ncbi.nlm.nih.gov/31575742/>

requires freezing of sperm and then artificially introducing it into the reproductive tract of a female during a specific window of time in her reproductive cycle. Therefore, sperm freezing and accurate detection of the window of female receptivity are crucial. These nuances are conducive for intensive livestock production systems such as the dairy industry in which >80% of dairy cattle are bred by artificial insemination. Indeed, the impact of this breeding approach on genetic makeup of dairy cattle in the U.S. has been a major contributor to the quadrupling of milk production per cow between 1950 and today.

In beef cattle production, use of artificial insemination has been limited, with only ~7% of animals being bred with the technology because of logistical disconnects. Most beef cattle are managed in range or pasture-based systems which do not allow for tracking the window of receptivity in females nor are they conducive with workforce needed to artificially inseminate large numbers of females. Natural breeding is the primary approach of most beef cattle production.

In swine production, although ~70% of pigs are bred using artificial insemination to influence genetic gain, survival of pig sperm during freezing is poor, thus the influence of elite genetics is regionally limited to regions and global dissemination is a challenge.

For all other livestock populations, such as goats and sheep, artificial insemination is not utilized widely due to need of specialized techniques; thus, introducing new genetics to improve production traits of populations worldwide has been marginal.

There has been lost opportunity to improve production traits for many livestock production sectors due to limited innovation in breeding technologies over the past several decades. Surrogate Sires technology was developed at Washington State University to address the unmet need of a novel tool that can be effectively applied in a natural breeding context to disseminate elite genetics in all livestock populations on a worldwide scale. The premise of the technology is transfer of stem cells that are responsible for continual sperm production from an elite male into the testicles of a battery of recipient males that lack their own sperm producing cells. The recipient males are then able to produce sperm containing the donor male's genetics and are used throughout the world in natural breeding schemes. This capability would provide the benefits of selective utilization of elite genetics without the need for intensive management practices or sperm cryopreservation. Moreover, the tool would be conducive with modern beef cattle, swine, and sheep/goat production practices.

Surrogate Sires technology relies on creating male livestock that lack their own sperm producing cells is to use CRISPR based gene editing to knockout a gene called NANOS2. The only known function of NANOS2 in all mammals that have been studied to date is for production of sperm producing cells. Therefore, gene edited NANOS2 knockout males are ideal Surrogate Sires. Importantly, recent peer-reviewed science has shown that following transplantation of donor sperm stem cells into testicles of a NANOS2 knockout male, sperm production commences, and all possess the non-edited genome of the donor. Thus, the offspring produced via natural breeding of the Surrogate Sire would not possess the gene edits created by CRISPRs. Moreover, the edits in the NANOS2 gene of the Surrogate Sire are mutations that could arise in nature.

Washington State University has established Investigational New Animal Drug (INAD) files with the Food and Drug Administration (FDA) for NANOS2 gene editing in multiple farm animal species to begin navigating the current U.S. federal regulatory approval process.

History of Regulatory Framework on Genetic Engineering of Food Animals in the US

Established by the White House Office of Science and Technology Policy (OSTP) in 1986, the Coordinated Framework for Biotechnology lays out the U.S. federal regulatory policy for how products derived from biotechnology are developed and introduced into the public domain. Composition and intended use are the basis of the Framework and a 1992 update reaffirmed that regulation should be based on the product and not the process by which the product was derived. The Framework does not assign biotechnology products to individual regulatory agencies or a single governing statute and as such, has evolved over time to assign primary jurisdiction of biotechnology oversight to the Food and Drug Administration (FDA), United States Department of Agriculture (USDA), or Environmental Protection Agency (EPA). Acts governing how agricultural biotechnology products are assigned to these federal agencies were established well before the advent of gene editing technologies. Thus, there is need to modernize the Coordinated Framework for Biotechnology in a manner that aligns with the state-of-the-art for how this area of science is being applied to livestock production today and into the future.

Within the U.S., multiple federal agencies have directives for regulatory jurisdiction over different aspects of livestock and the products they produce that could be impacted by the application of gene editing. As a means to mitigate the spread of diseases that affect livestock, the Animal Health Protection Act (AHPA) of 2002 established regulatory authority with the USDA Animal and Plant Health Inspection Service (APHIS) to oversee the importation and interstate movement of live animals in the U.S. Likewise, authority for monitoring safety of livestock products that are intended for human consumption has rested with the USDA Food Safety and Inspection Service (FSIS). Additionally, under the authority of the Federal Food, Drug, and Cosmetic Act (FFDCA), the FDA has authority for the safety of non-meat food and feed products derived from animals.

At present, as assigned by the FFDCA, regulatory oversight of genetically modified animals in the U.S. rests with the FDA. Through interpretation of this authority, substances other than food that affect the structure/function of an animal are considered to be a drug. As such, the molecular elements such as DNA that alter the genome of an animal are considered a drug. In this manner, gene editing approaches are channeled into a regulatory approval process that is not well matched for how the technology alters the genome, is transmitted to subsequent generations, or the intended purposes. At present, developers of a gene editing application in livestock must undergo an Investigation New Animal Drug (INAD) process during early-stage proof-of-concept and the full New Animal Drug Application (NADA) process in order to achieve commercialization and use in the public domain. Both these processes were designed for development of actual drugs and not for hereditary changes in the genome.

A Need for Modernization of Regulatory Framework

In 2017, draft Guidance for Industry (GFI) #187: Regulation of Intentionally Altered Genomic DNA in Animals was issued by the FDA for framework that regulates approval and oversight function of genetically altered livestock⁸. GFI #187 considers gene editing technologies as animal drugs and does not discriminate from genomic changes that could arise in nature (e.g. insertions, deletions, rearrangements, and single nucleotide polymorphisms) versus those that are novel and generated only through a genetic engineering process (e.g. use recombinant DNA and transgenesis). Of note, the long-standing practice of selective breeding results in the creation of genomes by way of human intervention and therefore can be considered as intentional genomic

⁸ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-187-regulation-intentionally-altered-genomic-dna-animals>

alterations in animals. Yet, this common practice in animal breeding is not regulated by the FDA or any other federal agency.

In 2021, the USDA and officials of the Department of Health and Human Services (HHS) signed a Memorandum of Understanding (MOU) for the FDA and USDA to collaborate on shaping a modernized federal regulatory framework that would streamline a cost-effective approach to approving and monitoring gene editing in domestic animals⁹. Under authority of the AHPA and Federal Meat Inspection Act, the MOU proposes that the USDA would establish a rulemaking process for pre-market evaluation and post-market monitoring of safety concerns related to both human and animal health for genetic engineering applications, including gene editing, in agricultural species. The MOU also lays out how the FDA would retain jurisdiction of intentional genomic alterations in animals intended for purposes other than agricultural use. Moreover, the MOU calls for collaboration between the USDA and FDA in fully vetting safety and health concerns that are not clearly addressable by the streamlined USDA evaluation process. I fully support this MOU and the accompanied Advanced Notice of Proposed Rulemaking (ANPR) on regulating the movement of animals modified or developed by genetic engineering posted by the USDA in 2020.

Because the science and technology of genetic engineering and potential applications in domestic animals is complex, ranging from generation of novel biomedical models to gene therapy to enhancing traits for the improvement of animal agriculture, assigning federal regulatory jurisdiction to a single agency is challenging and could stymie innovation. The current state for federal evaluation, approval, and monitoring of intentionally genetically altered animals in the U.S. are based on processes established for transgenic technologies which do not align well with the state-of-the-art gene editing technologies. In addition, these processes are viewed by many developers of genetic engineering applications in livestock as ambiguous, glacial in pace, and cost prohibitive.

The House Committee on Agriculture has recognized the importance of navigating this regulatory process with the recent letter signed by many members of the subcommittees asking Secretary Vilsack and Commissioner Woodcock to address this issue with a timely improved regulatory process. Thank you for your leadership.

A Call to Action by the AAVMC/APLU Task Force on Gene Editing of Livestock

In 2020, a task force on gene editing of livestock was assembled by joint efforts of the AAVMC and APLU as an effort to generate a blended, yet cohesive, perspective on how applications of gene editing in livestock could be regulated within the U.S. WSU leadership worked with colleagues in the AAVMC and APLU to establish the task force and charge it with addressing mutual interests of the developer, federal regulatory entities, animal, and consumer. To this end, a group of academicians with international reputation as experts in the science of animal genetic engineering, commercial sector representatives, engagement specialists, and animal bioethicists were assembled as a thinktank. The task force was effective in melding of perspectives voiced by these groups into a series of recommendations that were provided to federal regulators for

⁹ <https://www.aphis.usda.gov/biotechnology/downloads/mou-usda-fda.pdf>

consideration when envisioning what a modernized and progressive framework for the regulation of gene edited livestock in the U.S. should be¹⁰.

Conclusion

George Washington once wrote that, “I know of no pursuit in which more real and important services can be rendered to any country than by improving its agriculture, its breed of useful animals, and other branches of a husbandman's cares”. This statement was relevant 200 years ago and still rings true today. The U.S. has been providing leading edge innovation in animal agriculture for nearly 100 years and the next frontier in devising strategies to effectively feed a growing global human population will be defined by gene editing technologies. Harmonization of the regulatory processes beyond the U.S. is key and the regulatory community across the globe look towards the U.S. for stewardship and leadership. For the U.S. to remain as a world-wide leader in shaping how livestock products are produced in sufficient quantity to be cost-effective sources of high-quality protein in the human diet, the federal regulatory landscape for approving and monitoring of genetic engineering applications must evolve and align with the interests of the developer and consumer. To this end, a coordinated assessment and approval process between the USDA and FDA will be essential in establishing a framework that is streamlined, cost-effective, and ensures safe food, with the decision-making process anchored on logic and science-based fact. Humans have been consuming animal products with mutations in DNA that arose naturally and were propagated by way of selective breeding for thousands of years. Thus, developing a regulatory channel for approval of animals possessing gene edits that could have arisen in nature as safe for human consumption should be considered.

Thank you for the opportunity to testify before this panel today and I would be glad to address your questions.

¹⁰ <https://www.aavmc.org/wp-content/uploads/2021/07/AAVMC-Gene-Editing-Report-12.pdf>