Proc. Assoc. Advmt. Anim. Breed. Genet. 26: 1-5

GLOBAL REGULATIONS GOVERNING GENOME EDITING IN FOOD ANIMALS

A.L. Van Eenennaam

Department of Animal Science, University of California -Davis, California, 95616
United States of America

SUMMARY

With the emergence of genome editing (GnEd), many countries are considering regulatory approaches that allow GnEd organisms that could have been developed through conventional breeding to be regulated under the same rules as conventionally-bred organisms, rather than as genetically modified organisms (GMO). However, this approach has not been universally adopted, and given the importance of international trade in agricultural products, the most risk-adverse policy (e.g. all GnEd animals are *a priori* regulated as GMOs, irrespective of the nature of the edit) may end up becoming the de facto global standard. This is a form of "risk colonialism", whereby precaution-based regulations to a biotechnology in one country effectively precludes or disincentives the adoption of that biotechnology by trading partners for fear of losing market access.

INTRODUCTION

The purported purpose of animal biotechnology regulations is to protect human and animal health and the environment. The high cost and unpredictable timeline for the approval of genetically modified organisms (GMOs) have effectively forestalled the commercialization of animal biotechnology products, especially in Europe (Lubieniechi *et al*. 2025). Despite active research on introducing valuable traits via recombinant DNA technologies in the late 1990s and early 2000s, only two genetically engineered food animals have been approved for food use in the world; the AquAdvantage Atlantic salmon, and the GalSafe pig, and neither can be grown on conventional farms. There are substantial opportunity and economic costs associated with delaying the adoption of safe breeding innovations in animal breeding programs (Van Eenennaam *et al.* 2021).

GnEd refers to making a targeted alteration to the genome using site-directed nucleases. Typically, this involves introducing a double stranded break (DSB) in the DNA helix which can then be repaired by the non-homologous end joining (NHEJ) pathway, or in the presence of a nucleic acid repair template flanked by DNA sequences homologous to the sequence on either side of the DSB, using the homology-directed repair (HDR) pathway. The latter can involve a template that contains DNA sequences from sexually-compatible organisms (cisgenic), or from other species (transgenic). Animals that are descended from a GnEd parent that do not inherit the genetic edited sequence themselves are called null segregants (e.g. 50% of offspring from a hemizygous animal).

The current status of global regulations of GnEd animals is summarized in Table 1 and was largely drawn from Wray-Cahen *et al*. (2024). Some regions are using an arbitrary classification of genome edits categorized as site-directed nuclease (SDN) -1,2,3 differentiated by the size and nature of the edit. SDN-1 edits are defined as those that involve simple NHEJ deletions and insertions and no nucleic acid repair template. Distinctions between the remaining SDN classes are not clear-cut, notably between "short" and "long" nucleic acid repair templates, and "novel" and "foreign" DNA.

Table 1. Global approaches to regulation of genome editing (GnEd) animals, and whether GnEd food animal applications have been received. Modified from Wray-Cahen *et al.* (2024)

Country	Policy	No nucleic acid template	Short[a] nucleic acid template	Long nucleic acid template	Foreign DNA Synthetic/ Transgenic	Null Segregant	Decisions made for GnEd Animal?
Central and South America							
Argentina	Resolution 21/2021	Not GMO	Not GMO	Likely not GMO[b]	GMO	Not GMO	Yes
Brazil	Normative Resolution 16	Not GMO	Likely not GMO	Likely not GMO	GMO	Not GMO	Yes
Colombia	Resolution No. 22991	Not GMO	Not GMO	Likely not GMO	GMO	Not GMO	Yes
Uruguay	Decree No. 84/024	Not GMO	Likely not GMO	Likely not GMO	GMO	Not GMO	No
North America							
Canada	Novel Foods Laws (product based)	Method of genetic modification does not determine whether safety assessment is required; "novelty" of product is regulatory trigger for pre-market assessment					No
USA	Coordinated Framework (GFI #187 A/B)	Intentional Genomic Alterations (IGAs) evaluated on case-by-case basis. May grant "enforcement discretion" for low-risk products				Not GMO	Yes
Asia and Oceania							
Australia	Environmental release	Not GMO	GMO	GMO	GMO	Not GMO	No
Australia/ New Zealand	Proposal P0155 (FSANZ)	Not GMO	Likely not GMO	Likely not GMO	GMO	Not GMO	No
New Zealand	Current legislation	GMO	GMO	GMO	GMO	Not GMO	No
	Proposed legislation	Not GMO	Risk-tiering system proposed		GMO	Not GMO	
Indonesia	Draft proposal	Not GMO	Not GMO	Likely not GMO	GMO	Not GMO	
Japan	MAFF – environment	Not GMO	GMO	GMO	GMO	Not GMO	
	MAFF- Animal Products	Not GMO	Likely not GMO	Likely GMO	GMO	Not GMO	Yes
	Ministry of Health, Labor and Welfare	Not GMO	Likely not GMO	Likely GMO	GMO	Not GMO	
Africa and Middle East							
Ghana, Kenya, Malawi		Not GMO	Not GMO	Not GMO	GMO	Not GMO	No
South Africa	GMO Act of 1997	GMO	GMO	GMO	GMO	Undetermined	No
Europe							
EU	Directive 2001/18/EC	GMO	GMO	GMO	GMO	Not GMO	No
Norway	Proposed	Not GMO	GMO	GMO	GMO	Not GMO	No
	Proposed	Not GMO	Expeditated Assessment		GMO		
UK	Awaiting establishment of animal welfare provisions	Not GMO	Not GMO	Not GMO	GMO	Not GMO	No

[a] Defined by some countries as no more than 20 bp [b] Perfect allele replacement

The GnEd food animal applications that have undergone a regulatory process in at least one country are listed in Table 2 (Retrieved from https://www.isaaa.org/animalbiotechdatabase, 4/1/2025). These applications do not include a "new combination of genetic material", also known as transgenic DNA. Food products from three GnEd fish species have already reached the consumer marketplace in Japan. Kyoto University-based start-up, Regional Fish Co., Ltd., started selling GnEd red sea bream, tiger pufferfish, and olive flounder shortly after these applications were first reported in the scientific literature in 2018 and 2019, following determination by Japanese regulatory authorities that the deletions that occurred in the target gene in these GnEd fish were 'non-GMO'.

Table 2. GnEd animals that have undergone a regulatory determination in different countries

Country	Common name	Trait	Developer	Gene Targeted	Year
Argentina	Nile Tilapia	Increased yield	AquaBounty	Myostatin	2018
	Beef cattle	Heat tolerance	Acceligen	Prolactin receptor	2020
	Dairy cattle	Heat tolerance /Polled	Acceligen	Prolactin receptor /Pc Polled allele	2020
	Cattle	Increased yield	Acceligen	Myostatin	2021
	Other species (?)	Unknown as disclosure is not needed for non-GMO products			
Brazil	Nile Tilapia	Increased yield	AquaBounty	Myostatin	2019
	Beef cattle	Heat tolerance	Acceligen	Prolactin receptor	2021
	Dairy cattle	Heat tolerance	Acceligen	Prolactin receptor	2023
	Cattle	Increased yield	Acceligen	Myostatin	2021
	Pig	PRRS[a]-resistance	Genus, plc	CD-163	2024
Colombia	Pig	PRRS-resistance	Genus, plc	CD-163	2023
Japan	Red Sea Bream	Increased yield	Regional Fish	Myostatin	2021/22
	Tiger Pufferfish	Faster growth	Regional Fish	Leptin receptor	2022
	Olive Flounder	Faster growth	Regional Fish	Leptin receptor	2023
USA	Beef Cattle	Heat tolerance	Acceligen	Prolactin receptor	2022

[a] Porcine Reproductive and Respiratory Syndrome (PRRS) virus.

DISCUSSION

The introduction of useful GnEd alleles into livestock breeding programs will require a regulatory approach that is fit-for-purpose, meaning that safe products can come to market in a timely fashion and the regulatory evaluation timeline is compatible with the pace of the breeding program. As can be seen in Table 2, countries that are treating simple edits with no template guided repair as analogous to conventionally-bred animals, have already made regulatory decisions that allow products to come to market. Interestingly, the commercialization of the three GnEd fish species in Japan did not result in the anticipated consumer pushback. Efforts by groups opposed to GnEd did not gain traction, and media coverage was mostly positive (Matsuo and Tachikawa 2022).

Genus, plc has announced plans for its subsidiary the Pig Improvement Company, to introduce the PRRS-resistance allele lacking exon 7 of CD163 into its four elite grandparent swine breeding lines (two maternal & two paternal) in the homozygous condition, with the ultimate objective of producing commercial pigs that are resistant to Porcine Reproductive and Respiratory Syndrome (PRRS) virus (Burger *et al.* 2024). A requirement of any breeding program is to maintain sufficient genetic diversity for future genetic progress, meaning that in this case the edit had to be introduced into multiple founder breeding boars and gilts (10–15 per line). Illumina short amplicon sequencing was employed to screen 435 founder animals to identify the 90 (35 boars, 55 gilts) that had the intended edit, as well as screen for other unintended alterations within, or immediately adjacent to, the targeted CD163 locus. This was complemented by Oxford Nanopore Technologies sequencing of 2.8 kb PCR amplicons to evaluate the structural integrity around the target. Characterization of

the intended edit, along with robust phenotyping of GnEd animals for production traits and in this specific example the PRRS disease resistance phenotype, was undertaken by the breeding company.

Unique to GnEd animal evaluations is this requirement to identify potential off-target mutations, defined as an edit at a location on the genome that is not the intended target. Even though Genus, plc is a large multinational company, using whole genome sequencing (WGS) on this large number of founder animals was not seen to be cost-effective off-target screening tool for large numbers of founders. Therefore, the SITE-Seq® assay was used to identify a total of 182 putative off-target sites associated with the dual guide RNAs used in to delete exon 7 of CD163. This was validated with WGS on a small number (n=24) of edited pigs and their progeny. WGS identified 63 *de novo* mutations in GnEd animals, compared with 80 in wild type animals. Given the GnEd pigs were otherwise healthy, it is unclear what purpose is served by requiring the identification of de novo mutations in GnEd animals, when such analyses are not required for conventionally-bred animals.

The value and purpose of de novo variation identification in GnEd animals needs to be given serious consideration, given it is difficult to envisage a path to harm associated with de novo mutations that do not manifest as a phenotype. Genetic variation *per se* in an otherwise healthy animal is not a food safety hazard. Further, animal breeders have been safely making genetic improvement by selecting on uncharacterized de novo mutations for centuries. We reported that unedited commercial rams in our campus flock had on average 5.1 million naturally-occurring SNP and indel mutations relative to the Rambouillet sheep reference genome (Mahdi *et al.* 2025). Similarly, the 1000 bull genome project sequenced 2,703 cattle of different breeds and found 84 million SNPs and 2.5 million naturally-occurring indels (Hayes and Daetwyler 2019). This variation drives genetic progress in breeding programs, and animals produced by conventional breeding methods are not routinely evaluated for de novo mutations at the molecular level. The food safety benefit resulting from expensive and time-consuming off-target analysis on the genomes of healthy GnEd animals is therefore unclear against this well-documented background of genetic variation.

The livestock breeding community is uniquely positioned to provide substantive and evidence-based comments regarding proposed regulatory approaches and data collection requirements for GnEd animals for agricultural purposes. Necessitating the documentation of all potential off-target edits uniquely for GnEd animals in the absence of a path to harm will increase the cost of using this technology in commercial breeding programs, with no clear benefit to public health and safety.

CONCLUSION

Many countries are currently developing regulatory frameworks for GnEd animals and their products. History shows that the expensive and overly precautionary regulatory approaches that were associated with GMO animals were not fit-for-purpose and had a chilling effect on investment and adoption of this technology in animal breeding programs. The animal breeding community has an opportunity to provide evidenced-based input to help ensure that emergent regulatory frameworks for GnEd animals are science-based, risk-proportionate, and focused on novel hazards associated with GnEd. Well-considered policies should enable safe products to reach the market, and permit the cost-effective incorporation of biotechnologies like GnEd into breeding programs and timelines.

ACKNOWLEDGEMENTS

I would like to acknowledge the support of AAABG in providing travel funding to allow me to attend the 26th AAABG conference in New Zealand. My program receives funding from USDA Foreign Agricultural Service Cooperative Agreement FX23TA-10960C036 “Virtual and in-Person Workshops on Regulatory Aspects of Genome Editing in Animal Biotechnology Development”

REFERENCES

Burger B.T., Beaton B.P., Campbell M.A., *et al.* (2024) *CRISPR J.* **7**: 12.

Hayes B.J. and Daetwyler, H.D. (2019) *Annu Rev Anim Biosci.* **7**: 89.
Lubieniechi S.A., Van Eenennaam A.L. and Smyth S.J. (2025) *Trends Biotechnol*. **43**: 511.
Mahdi A.K., Fitzpatrick D.S., Hagen D.E., *et al.* (2025) *CRISPR J*. **8**: 13.
Matsuo M. and Tachikawa M. (2022) *Front. Genome Ed.* **4**: 899154.
Van Eenennaam A.L., De Figueiredo Silva F., Trott J.F. and Zilberman D. (2021) *Annu. Rev. Anim. Biosci.* **16**: 453.
Wray-Cahen D., Hallerman E. and Tizard M. (2024) *Front. Genome Ed*. **6**: 1467080.