Trends in Biotechnology

Focus Issue: 50 years after Asilomar

Opinion

Regulation of animal and plant agricultural biotechnology

Simona A. Lubieniechi [2,*], Alison L. Van Eenennaam [1,3,@], and Stuart J. Smyth [2,@,4]

Fifty years ago, scientists developed a regulatory framework for the safe use of recombinant DNA that focused on potential biosafety risks associated with the products of genetic engineering (GE). This morphed into an expensive and lengthy premarket risk assessment requirement for GE agricultural biotechnology products triggered solely by the fact that modern molecular technologies were involved in the development of those products. This has limited the commercialization of GE crop products primarily to multinational enterprises and precluded the development of GE animals at scale. Gene editing offers an opportunity to rethink the regulation of agricultural biotechnologies, and several countries have determined that gene-edited products lacking any 'foreign' DNA will be treated in the same way as products of conventional breeding.

Highlights

The Asilomar Conference created recombinant DNA research guidelines that were expanded to agbiotech.

The Cartagena Protocol on Biosafety specifically flagged organisms possessing 'a novel combination of genetic material obtained through the use of modern biotechnology' for unique regulatory scrutiny, irrespective of product risk.

The resulting process-triggered regulatory frameworks for agbiotech products have proven to be a prohibitively expensive obstacle, precluding many beneficial products from coming to market.

The economic and environmental opportunity costs of precluding access to safe innovations is high as genetic improvement is a key driver of agricultural sustainability.

Given the long safety record of plant and animal breeding, agbiotech product regulation should be updated to be agnostic to process, triggered by novel product risks, if any, and proportionate to risk.

Grounding risk appropriate regulations

In February 1975, scientists involved in the initial **recombinant DNA (rDNA)** (see Glossary) experiments met in Asilomar, California engaging in a thorough discussion of this emerging technology. Research experts gathered to share concerns, evidence, insights, and best scientific practices. The Asilomar Conference created guidelines on safe rDNA experiment conduct, subsequently published by the American National Institutes of Health [1]. The **science-based** rDNA regulations that evolved assessed the **risks** of products resulting from **GE** technologies, not the process used to create the product.

Some countries implemented science-based, **product-based regulatory framework**, successfully commercializing GE crop varieties for 30 years, such as Canada where 147 GE crop varieties have been approved since 1995. Other countries adopted process-triggered risk evaluation frameworks and unpredictable approval timeframes which have proven to stifle innovation. These effectively precluded the successful commercialization of GE crops, such as in the European Union (EU), which has only approved one GE crop variety for cultivation since 2000 [2]. Moreover, the EU enacted a GE crop moratorium from 1999 to 2003, which was deemed illegal by the World Trade Organization, concluding there was no evidence to support EU risk claims. As agricultural biotechnology applications have expanded into increasingly diverse plant applications, as well as livestock, fish, and insects, some regulatory requirements have become increasingly onerous and costly, further slowing adoption.

Risk assessment and crop agriculture

In the late 1980s, regulatory systems began to develop in early GE adopting countries such as Canada and the USA. Substantial research was undertaken by scientists in these countries, along with the Organisation for Economic Cooperation and Development (OECD), that fully explored potential risk assessment factors, such as gene flow, allergenicity, toxicity, invasiveness,

[1]Department of Animal Science, University of California, Davis, CA, USA
[2]Department of Agricultural and Resource Economics, College of Agriculture and Bioresources, University of Saskatchewan, Saskatoon, SK, Canada
[3]https://animalscience.ucdavis.edu/people/faculty/alison-van-eenennaam
[4]www.saifood.ca

*Correspondence:
sal446@usask.ca (S.A. Lubieniechi).
@X: @BioBeef (A.L. Van Eenennaam) and @stuartsmyth66 (S.J. Smyth).

impact on non-target organisms, etc. This resulted in 1186 science publications that underpinned the global risk assessment framework for biotechnology [3]. This scientific robustness has been confirmed through the subsequent 4485 risk assessments undertaken since 1992 by regulatory agencies in the 29 GE producing countries and the 43 GE crop importing countries, all concluding the risks from commercialized GE crops do not differ from the risks of comparable non-GE crops (https://www.isaaa.org/resources/publications/briefs/55/executivesummary/default.asp). An extensive study by the National Academies of Sciences, Engineering, and Medicine found no substantiated evidence of a difference in risks to human health between current commercially available GE crops and conventionally bred crops, nor did it find conclusive cause-and-effect evidence of environmental problems [4].

GE crops were first commercialized in the mid-1990s in Argentina, Canada, and the USA, using science-based regulatory frameworks. Such regulatory frameworks were subsequently adopted by other countries, including Australia, Brazil, and South Africa, as GE technologies became more widely adopted. However, due to the substantial regulatory approval times and costs, these regulatory expenses were largely only economically manageable for multinational enterprises (MNEs) developing broad-acreage crops like canola, corn, cotton, and soy. In 2019, less than 2% of the 190 million global GE crop hectares were of varieties other than those four crops (https://www.isaaa.org/resources/publications/briefs/55/executivesummary/default.asp). A small number of GE crops were developed and commercialized by public institutions prior to 2000, such as flax at the University of Saskatchewan [5] and papaya by the US Department of Agriculture [6]. As commercial production regulatory approval costs soared past $100 million (https://croplife.org/wp-content/uploads/2022/05/AgbioInvestor-Trait-RD-Branded-Report-Final-20220512.pdf), public developers, along with small and medium sized enterprises (SMEs), were forced out of the technology development market.

MNE commercialization domination is evidenced by GE crop approvals in Canada and Argentina. Argentina's regulatory approvals were 90% foreign MNEs, 8% domestic firm and/or public institution, and 2% foreign SME [2]. The vast majority (89%) of **plants with novel traits (PNTs)**, which is Canada's term that includes GE crops, were developed by MNEs (Table 1). Of 147 PNT applications, just 15 (10%) belonged to SMEs and only one was developed by public breeders. The prohibitive costs for getting a PNT approved resulted in a significant disadvantage for public breeders, as well as for SMEs. Not only were costs prohibitive, but space was limiting as research organizations needed physically separate spaces to undertake PNT and conventional variety development. There have been a small number of GE crops from public developers in developing countries, including eggplant (brinjal) in Bangladesh, cotton in Burkina Faso, cowpea in Nigeria and Ghana, as well as from smaller seed companies, such as GE cotton varieties commercialized in India.

While GE crop production had expanded to 29 countries by 2019 (https://www.isaaa.org/resources/publications/briefs/55/executivesummary/default.asp), the technology's full potential

Table 1. GE crop approvals in Argentina and Canada[a]

Developers	Argentina	Canada
Multinational enterprises	90%	89%
Foreign small- and medium-sized enterprises	2%	5%
Public institutions and domestic SMEs	8%	6%

[a]Modified from [2] and https://inspection.canada.ca/en/plant-varieties/plants-novel-traits/approved-under-review/decision-documents.

is estimated to only be one-third of what might have been achieved had regulations been risk appropriate [7]. The failure of regulatory approval is present in many markets, most notably the EU, where process-triggered regulations and precaution-based approvals prevail [8]. The EU's approach has had far reaching implications, particularly in Africa and Asia [9]. The EU initially followed the lead of Argentina, Canada, and the USA, allowing GE crop field trials, but a series of food safety failures in the late 1990s and the launch of aggressive campaigns from environmental activist organizations resulted in public concerns and regulatory frameworks that were not proportional to any potential product risk(s).

Since 2004, the regulation of GE crop use and release in the EU has been under the control of the European Commission (EC). First, each application is assessed by the European Food Safety Authority (EFSA) **Genetically Modified Organisms (GMO)** panel on a case-by-case basis. Following a favorable outcome, the application is then voted on by the Commission's Standing Committee on Plants, Animals, Food and Feed (PAFF), with representatives from all 27 Member States. A qualified majority voting system is applied, meaning approval requires 55% of Member States voting in favor and representing at least 65% of the total EU population [8]. Approval is therefore contingent on political factors rather than scientific assessment. The EU's process-triggered and precaution-based approval framework has stifled agricultural biotechnology innovation. Prior to the EU implementing their GE crop regulatory framework in 2004, one GE insect-resistant (Bt) corn variety (MON810) was approved for cultivation in 1998. This variety, as well as some derivatives produced by local breeders under license from Monsanto, is grown in Spain and Portugal and small areas of cultivation in Slovakia and the Czech Republic. However, since the genetics are now over 25 years old, production is declining as better genetics come to market. A second GE crop, a potato, was approved after 13 years of regulatory examination. Following these significant regulatory delays, the developer (BASF) withdrew the crop after 2 years of limited production [9].

Box 1. Revolution in carbon sequestration potential in crop agriculture

Over the past decade, countries have enacted policies and regulations designed to help reduce domestic GHG emissions as part of their commitments to achieving the Paris Accord's target of a 30% emission reduction by 2030, based on 2005 emission levels. Agriculture's potential in offsetting GHG emissions is considerable given plant carbon sequestration. While governments seek regulatory solutions to reducing GHG emissions, agricultural innovation offers tremendous potential for increasing carbon sequestration.

De Souza [43] applied GE technology to soybeans targeted at increasing the rate of photosynthesis. The resulting trials observed the soybean plants sequestered 10% more carbon, while increasing yields by an average of 24%. While this technology was tested in a small number of GE soybean plants, the promise is nothing short of revolutionary. Food crops that sequester carbon at increased rates, coupled with higher yields, contribute to achieving the Paris Accord as well as the United Nation's Sustainable Development Goals.

Innovation is foundational for mitigating the effects of climate change. The EU's rejection of GE crop technology results in GHG emissions that are higher by an estimated 33 million tonnes of CO_2 equivalents per year [36]. Additionally, the adoption of GM crops in Canada has resulted in tillage being used on only 3% of crop area in the province of Saskatchewan, compared with 74% of crop area is the EU [44]. Reduced tillage provides for reduced erosion, meaning that fewer chemicals and fertilizers enter into the local or regional watersheds. Moreover, it lowers the GHG emissions from crop production [45], further contributing to climate change mitigation.

Mitigating climate change and producing more consumable food is a technological solution that must not be stifled by risk inappropriate regulations. The Food and Agriculture Organization (FAO) (https://openknowledge.fao.org/items/445c9d27-b396-4126-96c9-50b335364d01) estimates that up to 783 million people were globally food insecure in 2023, a rise of 220 million from 2014. As climate variability increases, there is an increased potential for food production to be more adversely impacted by climate, meaning there is an urgent need for more innovative solutions. If science is truly going to be able to address the dual challenges of mitigating climate change and improving food security, then safe, beneficial technologies require science-based regulation based on any novel product attributes, not precaution-based regulation triggered by the use of a particular technology and implemented irrespective of product attributes.

Glossary

Gene editing (GnEd): also referred to as genome editing, alteration of the genetic material of a living organism by the targeted insertion, replacement, or deletion of a DNA sequence, typically with the aim of improving some characteristic, or correcting a genetic disorder.
Genetic engineering (GE): a process that uses modern molecular technologies, particularly those techniques referred to as recombinant DNA techniques, to alter the DNA makeup of an organism. Genetic engineering typically involves random introgression of a transgenic construct into a living organism's genome. GE has been used to produce human insulin, cancer therapies, brewing yeasts, and GE plants and livestock.
Genetically modified organism (GMO): a plant, animal, or microbe in which one or more changes have been made to the genome, colloquially used in reference to genetic engineering,
Hazard: something that has the potential to cause harm (e.g., a shark).
Plant with novel traits (PNTs): term used by the Canadian Food Inspection Agency to define a plant that contains a trait which is both new to the Canadian environment and has the potential to affect the specific use and safety of the plant with respect to the environment and human health. These traits can be introduced using biotechnology, mutagenesis, or conventional breeding techniques.
Precaution-based regulation: regulatory frameworks that apply the full discretion of the Precautionary Principle, whereby if the potential for adverse risks cannot be guaranteed to be zero, then denying commercial approval is the prescribed, and appropriate, regulatory decision.
Process-based regulatory framework: these frameworks assess the potential for risks triggered by the process that was used to produce a specific product, rather than any **hazard** attributes of the product itself.
Product-based regulatory framework: these frameworks assess the potential for risks triggered by the hazard attributes of a specific product, irrespective of the process used to produce it.
Recombinant DNA (rDNA): this technology involves using enzymes and various laboratory techniques to manipulate and isolate DNA segments of

The lack of approvals to cultivate GE crop varieties in the EU creates a competitive disadvantage for farmers, processors, traders, breeders, and consumers. European farmers are competing with GE crops but are unable to grow them. Agricultural biotechnology has led to increased global crop productivity and environmental benefits (Box 1), particularly for major producers such as the USA, Brazil, Argentina, and Canada. Since 1996, GE crops have generated an estimated US$261 billion in additional farm revenue from higher yields, but the vast majority of EU farmers have not shared any of these benefits [10]. Moreover, the use of GE insect resistant and herbicide tolerant crops from 1996 to 2020 reduced pesticide application globally by 748.6 million kg (–7.2%) of active ingredient [11,12] and allowed a shift to less toxic and persistent pesticides [13]. Table 2 highlights an annotated list of GE crop benefits.

Meanwhile, agricultural growth in the EU has stagnated given the lack of access to crop protection technologies and new seed varieties, resulting in the EU being import dependent, especially for livestock feed, which ironically is mostly GE varieties, resulting in a corn and soy trade deficit of over 10 million tonnes [14]. Moreover, the EU's regulatory system has resulted in the loss of billions in R&D investment. In 1995, one-third of global agricultural R&D investments were made in the EU, but by 2013 this figure had dropped to less than 8% (https://croplifeeurope.eu/rd-trends-for-chemical-crop-protection-products). EU GE crop research decreased by 90% from 2010 to 2016. Only 10 Member States currently permit GE field trials and only five (Belgium, Czech Republic, Romania, Spain, and Sweden) conducted open-field testing as of 2017 [14]. The lack of EU crop innovation technologies has resulted in crop productivity increases of a mere 7% from 1995 to 2019, compared with increases of 38% in the USA and 28% in Canada [15].

Risk assessment and livestock development

The mandatory premarket regulatory approval process for GE organisms, irrespective of product novelty or risk, has had an even more stifling effect on the development of GE animals. The first GE livestock were reported in 1985 [16] and several meritorious uses of the technology to improve livestock health [17–19] and reduce environmental impacts (e.g., EnviroPig) [20] were reported. However, as of late 2024, only two applications for food use have been approved globally: the fast-growing AquAdvantage salmon [21], and the hypoallergenic GalSafe pig on a limited basis (1000 pigs/year on a single facility) in the USA [22]. The AquAdvantage salmon was approved in the USA and Canada in 2015, and the GalSafe pig was approved in the US in 2020 after multidecadal regulatory journeys. The EnviroPig, expressing salivary phytase to breakdown phytate and decrease the phosphorus pollution potential of pig manure, developed by the University of Guelph, was not so fortunate with the application getting shelved after a prolonged regulatory attempt. There are a multitude of reasons for this lack of progress, including the fact that these applications were initially developed by public sector scientists and not MNEs, in combination with the high regulatory costs and unaccountable delays which have disincentivized

interest. This method can be used to combine (or splice) DNA from different species to create a transgenic construct with new functions.
Risk: the likelihood of harm occurring following exposure to a hazard. It is calculated by multiplying the probability of exposure to a hazard × the consequences (degree of harm) if exposure occurs. If exposure is zero (e.g., being on dry land), then by definition risk is zero, even though being in water with a hazardous shark has the potential to cause great harm.
Science-based regulatory framework: these frameworks are grounded in quantifiable scientific data to undertake a product risk assessment, which is then compared with the potential risks from the production of comparable, conventional products. If the potential for risk is equivalent, the product being assessed is approved for production.

Table 2. GE crop, country of cultivation, and documented benefits associated with cultivation over a specified period of time

Crop	Country	Benefit	Period of time	Refs
Cotton	India	Higher yield	2002–2008	[37]
Brinjal	Bangladesh	Higher yield and reduced insecticide use	2014–2018	[38]
Corn	Spain	Higher yield	1998–2021	[39]
Canola	Canada	Higher farmer profitability	1995–2007	[40]
Soybeans	Argentina	Higher yield, job creation	1996–2010	[41]
Corn	USA	Higher farmer profitability	1996–2009	[42]
Papaya	USA	Higher yield	2000–2009	[6]

research investment in this field [23]. Given the EU's arguably dysfunctional regulatory approval process, no GE livestock applications for food use have ever even been presented for regulatory approval in the EU (Box 2).

There have been limited approvals for pharmaceutical therapeutic proteins produced in GM animal milk and eggs in the EU and USA, but the animals themselves are not approved for food use. In three ironic cases, a GE goat (ATryn, GTC Biotherapeutics, USA) [24], rabbit (Ruconest, Pharming Group NV, the Netherlands) [25], and chicken (Sebelipase alfa, Alexion, USA) [26], the EU drug approvals for GE-animal product-derived therapeutic proteins in 2006, 2010, 2015, respectively, preceded the US drug approvals.

Ultimately, safe innovations to address very real problems of animal agriculture are delayed, or worse, even precluded from coming to market due to the high regulatory costs, with concomitant opportunity costs because the problem they were designed to address remains unresolved [23].

Risk appropriate gene editing regulations

Recently, the development of **gene editing (GnEd)** offers an opportunity for some potential relief from this arbitrary GE **process-based regulation** trigger. GnEd technology allows for targeted inactivation of endogenous loci through site-directed nucleases (e.g., CRISPR/Cas9) [27], resulting in many plants [28] and animals [29] produced not containing any 'transgenic' or foreign DNA. This has led some countries to reconsider their regulatory approach to simple edits, using a technique known as site directed nuclease 1 (SDN-1), where there is a targeted, non-specific genetic deletion mutation. In 2015, Argentina developed an approach for the regulation of new breeding techniques (NBTs), including GnEd, by determining whether the products were 'genetically modified organisms (GMOs)' [30]. The Cartagena Protocol on Biosafety (CPB) GMO definition was used, which must be adhered to by Convention on Biological Diversity signatory countries. The CPB defined a GMO (called 'living modified organisms' in the CPB) to mean 'any living organism that possesses a novel combination of genetic material obtained through the use of modern

Box 2. The opportunity cost of forgone livestock genetic innovation

Porcine reproductive and respiratory syndrome (PRRS) virus is a panzootic disease that causes suffering in pigs, including weight loss, fever, respiratory distress, and reproductive failure, resulting in high morbidity and high mortality. A decade ago, the annual cost of this disease was estimated to be more than USD$650 million in the USA and €1.5 billion in Europe [46]. Globally, the disease is estimated to cost the pork industry USD$2.7 billion annually. Genus plc (https://www.genusplc.com), a UK-based publicly traded animal genetics company, has announced its intention to bring the first GnEd PRRS virus-resistant pig to market [47]. These GnEd pigs are being produced by targeting an exon in a gene called *CD163* for deletion by introducing dual-guide sgRNAs and Cas9 ribonucleoproteins into zygotes from four genetically-diverse grandparental lines of pig [48].

Genus has indicated that it plans to seek regulatory approval in key markets, including Brazil, Canada, China, Colombia, Japan, Mexico, and the USA, prior to introducing the GnEd lines into their breeding program. They have already achieved non-GMO regulatory determinations in Brazil and Colombia [49]. They have also obtained approval to import PRRS virus-resistant pigs to China for an in-country regulatory assessment. The US FDA Center for Veterinary Medicine regulates any 'intentional genomic alteration' (IGA) in the genome of an animal using the same legal framework it uses to regulate new veterinary drugs. To obtain a new animal drug approval, Genus has opened an investigational new animal drug file and is performing studies to document the safety and effectiveness of the IGA. Genus expects to have a regulatory decision from the US FDA by 2025.

Notably, the company currently has no plans to seek approval to commercialize the PRRS virus-resistant pigs in Europe. The sustainability implications of this outcome can be assessed. The net present value of the costs associated with PRRS from 2020 to 2049 in the EU was estimated to be USD$28.86 billion [23]. Additionally, Genus has stated that they have commissioned a life-cycle assessment to approximate the environmental footprint of pork production using their genetic lines, with and without the PRRS virus-resistance. Finally, there are deleterious animal welfare outcomes associated with PRRS and the consequent need to treat sick animals with antimicrobial therapies. Jointly, these data will enable an analysis and consideration of the sustainability opportunity costs associated with forgoing PRRS virus-resistant pigs in the EU.

biotechnology' [30]. If the product does not include a new combination of genetic material (i.e., a stable and joint insertion of one or more genes or DNA sequences that are a part of a defined genetic construct) then it is treated no differently than products that result from conventional breeding, meaning it does not have to go through the GMO approval process.

As a result of this approach in Argentina, there has been an explosion of new product applications coming out of the public sector and SMEs. When comparing approved GMOs since 1996 to the determination of conventional or GMO status for products obtained using different NBTs through 2020, the entity developing the product went from 8% to 59% for local SMEs and public sector researchers, 2% to 32% for foreign SMEs, and the high 90% MNE rate decreased considerably to only 9% [2]. Moreover, the type of organisms in regulatory applications went from 0% GE animal approvals to over 25% of all NBT applications being either farm or aquatic animals (Figure 1).

Hearteningly, even though GnEd is a comparatively recent development compared with GE, food products from three GnEd animals have already reached the marketplace. Kyoto University-based startup SME, Regional Fish Co., Ltd., started selling GnEd red sea bream, tiger pufferfish, and olive flounder in Japan following determination by regulatory authorities that these GnEd fish were 'non-GMO'. In contrast to GE approvals, these applications were first reported in the scientific literature in 2018 and 2019, shortly prior to their sale as food. Table 3 provides a more general list of the GnEd animal applications that have undergone a regulatory process allowing some type of commercial sale. These products all have had a determination made by the relevant regulatory authority in the listed country that they are either low-risk (www.fda.gov/media/155706/download) or non-GMO (Argentina, Brazil, Colombia, Japan), and can be marketed.

There is no 'non-GMO' determination pathway for GnEd animals in the USA. Rather, the US Food and Drug Administration (FDA) has announced it will regulate GnEd animals on a case-by-case basis in the same manner as GE animals. The original guidance for industry #187 'Regulation of Genetically Engineered Animals Containing Heritable rDNA Constructs' was released in 2008, with an emphasis on any potential allergenic and toxic properties of the rDNA expression product. This guidance was subsequently revised in 2017, and again in 2024, and renamed '#187B Heritable Intentional Genomic Alterations in Animals: The Approval Process' (https://www.fda.gov/media/150658/download). The regulatory trigger was expanded from heritable rDNA constructs to an 'intentional genomic alteration' (IGA), which the FDA defines as 'changes to an animal's genomic DNA produced using modern molecular technologies, which may include random or targeted DNA sequence changes including nucleotide insertions, substitutions, or deletions.'

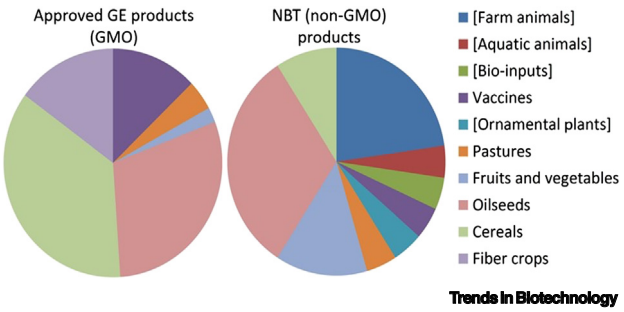

Figure 1. Approved genetically modified organisms (GMOs) (left) and new breeding techniques (NBT) (non-GMO) (right) product applications distributed by type of organism in Argentina (1996–2020). The NBT group includes farm and aquatic animals, along with a more diverse variety of plant species, including fruits and vegetables. Modified from [2] under a Creative Commons CC-BY-4.0 license. Abbreviation: GE, genetically engineered.

Table 3. 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.

This effectively categorizes any genetic variation in an animal made with 'modern molecular technologies' as a regulated article, irrespective of product risk. An accompanying document, "#187A: Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach' (https://www.fda.gov/media/150658/download), clarifies that developers of 'low-risk' IGAs in food animals (e.g., those that are equivalent to genomic sequences that are found in animals of the same species, or that could theoretically be achievable though conventional breeding resulting in no change in food composition), are required to provide premarket regulatory risk assessment data about the process used to generate the IGA, characterization of the genomic sequence, and information addressing animal safety, food safety, and risk of impacts on the environment, as appropriate for the intended use of the product. These data will be evaluated by the FDA to determine if the product is deemed 'low-risk' and can be marketed in the absence of an approval under 'enforcement discretion', meaning the FDA will not act against a developer for the introduction or delivery for introduction into interstate commerce of the IGA in that animal. The FDA clarifies that 'this is not a determination of "safety" under the Federal Food, Drug, and Cosmetic Act but is instead a determination that we understand the product's risks for the specified intended use and have concluded we have no safety concerns'.

In 2023, the FDA granted enforcement discretion for two GnEd PRLR-SLICK beef cattle, carrying an IGA in the prolactin receptor resulting in improved heat tolerance (Table 2). The risk assessment summary for these two animals (https://www.fda.gov/media/155706/download?attachment) concluded, 'Although the IGA in PRLR-SLICK cattle is not approved, conditionally approved, or index listed, because FDA has determined the IGA is low risk, at this time the agency does not intend to object to Acceligen marketing the IGA in PRLR-SLICK cattle or associated products derived from them (i.e., offspring, semen, or embryos) or introducing meat derived from the cattle containing this IGA into the food supply. This decision is limited to the marketed

products (e.g., live animals, semen, embryos, meat) derived from the existing two cattle containing the IGA for which FDA has reviewed data and their progeny.'

Such risk assessment evaluations are uniquely required for all food animals that have an intentional IGA resulting from the process of 'modern molecular technologies', but not for those associated with the millions of naturally-occurring genetic variants with presumably similar risk profiles that are the basis of conventional breeding programs [31]. This mandatory premarket risk assessment contrasts to the US approach for GnEd plants where no regulatory review is required in species that are not a plant pest, that could have been produced through conventional breeding methods, and that contain no foreign genetic material incorporated from a plant pest. Regulating 'intentional' genetic variation in GnEd animals as a drug, while turning a blind eye to the long safety record associated with the spontaneous-occurring genetic variation in our food producing species, is not a fit-for-purpose regulatory framework [32]. Moreover, there are other data that are being requested by some regulatory agencies regarding GnEd animals, including documentation of genome-wide off-target alterations, and evaluating environmental risks associated with release. However, analogous data (e.g., sequence data) are not required nor routinely collected for conventionally-bred food animals, raising the question as to why these data are uniquely required only for GnEd animals. Recently in Norway, researchers used GnEd to render Atlantic salmon infertile [33]. This was done in response to the fact that Norwegian wild Atlantic salmon strains are affected by interbreeding with farmed salmon that have escaped from net pens. However, it was deemed too risky to even undertake research to grow the sterile offspring of GnEd salmon in net pens in case some of the GnEd fish escaped [34]. Ironically, this precautionary approach to GnEd fish effectively paused research on a project that was designed to tackle the known risks associated with the ongoing genetic introgression of conventional farmed salmon into wild populations.

The problem with precaution-based regulation

Agricultural research over the past 40 years has clearly demonstrated science-based, product-risk focused regulatory frameworks are of fundamental importance to healthy, functioning innovation systems. Precaution-based and process-triggered regulatory approvals have consistently proven to be an innovation barrier. Many aspects of **precaution-based regulations** are grounded in the CPB and its allowance for socio-economic considerations (SECs) in regulatory evaluations. Most countries integrating SECs into their biotechnology regulatory frameworks have failed to commercialize any GE technologies as, in many instances, there are no robust methods capable of undertaking a SEC assessment, as well as a lack of data [35]. Precaution-based approval processes that integrate SECs have proven to be incapable of functioning in a way that allows safe products to come to market.

The lack of functioning regulatory frameworks will be a significant barrier as countries strive to meet their Paris Accord greenhouse gas emission (GHG) reduction targets. Scientific advances continually develop new products and technologies capable of improving agriculture sustainability and reducing GHG emissions, yet precaution-based regulatory systems prevent commercialization. Indeed, Kovak and colleagues [36] identified that had the EU adopted GE crop technologies at rates similar to that of Canada and the USA, then EU agricultural GHG emissions would be 7.5% lower (33MT of CO_2eq/year).

The CPB's role in stifling biotechnology innovation will not apply to many products of GnEd as the CPB only applies to organisms with a 'novel' combination of genetic material. We argue this arbitrary distinction is biologically meaningless, given the vast number of novel genetic combinations that are observed when comparing conventional organisms of the same species, also

known as genetic diversity. As Argentine regulations, and subsequent regulations in Brazil, Australia, Canada, Japan, and those for plants in the USA, have clearly established, the application of GnEd technologies that do not result in any 'foreign' DNA present in the commercialized product will be viewed as conventional breeding and not subject to additional GMO regulations. In Argentina, this has resulted in a sevenfold (8% to 59%) increase in the proportion of products from local SME and public sector developers [2]. Removing the financial costs and time delays from the regulatory approval process is accelerating innovation rates. African and Asian countries are additionally beginning to follow Argentina's lead, determining that GnEd plant and animals with nucleic acid repair template-free genetic mutations (i.e., SDN-1) are not GMOs and do not need to be regulated as such.

In March 2015, the EC proposed a new Cultivation Directive GE crop authorization for Member States. This allowed Member States to 'opt-out' of allowing cultivation or import of an approved GE crop without the need for scientific justification. Thereafter, 15 Member States (Austria, Bulgaria, Croatia, Cyprus, Denmark, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Netherlands, Poland and Slovenia) and the regions of Scotland, Northern Ireland, Wales and Wallonia told the EC they would opt out of allowing GM crop cultivation [8]. The EU is presently locked in a political stalemate as to how, or whether, to regulate GnEd technologies. The first field trial of fungus-resistant GnEd rice in Italy was completely destroyed by environmental activists in June 2024 (https://www.science.org/content/article/landmark-gene-edited-rice-crop-destroyed-italy).

Hungary assumed the rotating 6-month EU presidency on 1 July 2024, with Poland assuming the role on 1 January 2025. Neither nation has expressed support for GnEd in agriculture. Subsequent president countries starting 1 July 2025 through 30 June 2029 are Denmark, Cyprus, Lithuania, Greece, Italy, Latvia and Luxembourg, respectively. Likewise, none of these countries have publicly indicated support for GnEd technologies in the EU to be regulated similar to the approach pioneered by Argentina, suggesting, in our opinion, that any regulatory certainty or clarity regarding GnEd food plants and animals in the EU will be unlikely for virtually the rest of this decade. If the EU decides GMO approval is required to allow the import of GnEd organisms, similar to that which exists for GE crops, the EU may find itself fenced-out of most global commodity trade, as the rate of adoption of GnEd technologies is steadily increasing. Additionally, few countries plan to label or track GnEd products as they are being treated as, and are often indistinguishable from, conventionally-bred products. This may leave the EU with no option but to reject imports if it is unable to know with certainty whether unapproved GnEd commodities are present in a shipment.

Concluding remarks

The data required for the regulatory approval of the products of animal and plant biotechnology have expanded considerably from the biosafety considerations discussed by Asilomar delegates, concomitantly raising both incurred regulatory and opportunity costs. Global regulatory costs for a single biotechnology event exceed $USD 100 million and it has been difficult, if not impossible, to obtain cultivation approvals in the EU. Decoupling science-based risk assessment from variety approval has proven to be a failure. This has precluded or disincentivized commercialization of many beneficial GE applications.

A better regulatory regime for plant and animal biotechnology would be guided by novel attributes of the product, if any, rather than triggered by the process used to develop that product. Currently, regulatory reviews concentrate only on risks associated with new varieties, ignoring both risks associated with existing varieties and the benefits ensuing from the primary purpose for

Outstanding questions

What can be done to facilitate regulatory decision making away from precaution-based regulation?

What is driving the movement away from evidence-based regulation?

Is zero risk achievable? If not, how can safety thresholds, established by science to ensure consumers are safe, be better communicated?

In regulatory frameworks, should the science-based risk assessment process be decoupled from the variety approval process?

Is the objective of regulations to prevent any level of risk from occurring?

the invention. Risk assessments should balance unique risks associated with new varieties against offsetting benefits (see Outstanding questions). Moreover, products that could have been achieved using conventional breeding should not be held to different standards or require regulatory studies beyond those required for products derived from conventional breeding. Finally, following submission of all predefined required data, finite response times for agency decisions should be imposed to provide developers and investors with a predictable regulatory approval timeline. No industry can survive a protracted and unpredictable regulatory path to market. The uncertainty and significant regulatory costs surrounding agricultural biotechnology are currently impeding the commercialization of beneficial varieties that could help to sustainably address both present and future food security needs.

Declaration of interests

No interests are declared.

References

1. Berg, P. and Singer, M.F. (1995) The recombinant DNA controversy: twenty years later. *Proc. Natl. Acad. Sci. U. S. A.* 92, 9011–9013
2. Whelan, A.I. *et al.* (2020) Gene editing regulation and innovation economics. *Front. Bioeng. Biotechnol.* 8, 303
3. Gleim, S. and Smyth, S.J. (2018) Scientific underpinnings of biotechnology regulatory frameworks. *New Biotechnol.* 42, 26–32
4. National Academies of Sciences, Engineering, and Medicine (2016) *Genetically Engineered Crops: Experiences and Prospects*, The National Academies Press
5. Ryan, C. and McHughen, A. (2014) Tomatoes, potatoes and flax: exploring the cost of lost innovations. In *Handbook on Agriculture, Biotechnology and Development* (Smyth, S.J. *et al.*, eds), pp. 841–852, Edward Elgar Publishing
6. Gonsalves, C.V. and Gonsalves, D. (2014) The Hawaiian papaya story. In *Handbook on Agriculture, Biotechnology and Development* (Smyth, S.J. *et al.*, eds), pp. 642–660, Edward Elgar Publishing
7. Hansen, C.W. and Windender, A.M. (2023) National and global impacts of genetically modified crops. *Am. Econ. Rev. Ins.* 5, 224–240
8. Halford, N.G. (2019) Legislation governing genetically modified and genome-edited crops in Europe: the need for change. *J. Sci. Food Agric.* 99, 8–12
9. Smyth, S.J. (2017) Genetically modified crops, regulatory delays, and international trade. *Food Energy Secur.* 6, 78–86
10. Smyth, S.J. *et al.* (2014) Investment, regulation, and uncertainty: managing new plant breeding techniques. *GM Crops Food* 5, 44–57
11. Brookes, G. (2022) Genetically modified (GM) crop use 1996–2020: environmental Impacts associated with pesticide use change. *GM Crops Food* 13, 262–289
12. Lika, E. *et al.* (2024) Quantifying changes in the environmental impact of in-crop herbicide use in Saskatchewan, Canada. *Weed Technol.* 38, e28
13. Kniss, A. (2017) Long-term trends in the intensity and relative toxicity of herbicide use. *Nat. Commun.* 8, 14865
14. Hundleby, P.A.C. and Harwood, W.A. (2019) Impacts of the EU GMO regulatory framework for plant genome editing. *Food Energy Secur.* 8, e00161
15. Paarlberg, R. and Smyth, S.J. (2023) The cost of not adopting new agricultural food biotechnologies. *Trends Biotechnol.* 41, 304–306
16. Hammer, R.E. *et al.* (1985) Production of transgenic rabbits, sheep and pigs by microinjection. *Nature* 315, 680–683
17. Bleck, G.T. *et al.* (1998) Production of bovine alpha lactalbumin in the milk of transgenic pigs. *J. Anim. Sci.* 76, 3072–3078
18. Maga, E.A. *et al.* (2006) Human lysozyme expressed in the mammary gland of transgenic dairy goats can inhibit the growth of bacteria that cause mastitis and the cold-spoilage of milk. *Foodborne Pathog. Dis.* 3, 384–392
19. Wall, R.J. *et al.* (2005) Genetically enhanced cows resist intramammary *Staphylococcus aureus* infection. *Nat. Biotechnol.* 23, 445–451
20. Golovan, S.P. *et al.* (2001) Pigs expressing salivary phytase produce low-phosphorus manure. *Nat. Biotechnol.* 19, 741–745
21. Du, S.J. *et al.* (1992) Growth enhancement in transgenic Atlantic salmon by the use of an all-fish chimeric growth-hormone gene construct. *Nat. Biotechnol.* 10, 176–181
22. Lai, L. *et al.* (2002) Production of alpha-1,3-galactosyltransferase knockout pigs by nuclear transfer cloning. *Science* 295, 1089–1092
23. Van Eenennaam, A.L. *et al.* (2021) Genetic engineering of livestock: the opportunity cost of regulatory delay. *Annu. Rev. Anim. Biosci.* 9, 453–478
24. Meade, H. (2008) The approval of ATryn®, the first commercial recombinant form of human antithrombin. In *Biosafety Research of GMOs: Past Achievements and Future Challenges, Symposium Handbook*, pp. 57, 10th International Symposium on the Biosafety of Genetically Modified Organisms
25. Moldovan, D. (2015) Recombinant replacement therapy for hereditary angioedema due to C1 inhibitor deficiency. *Immunotherapy* 7, 739–752
26. Shirley, M. (2015) Sebelipase alfa: first global approval. *Drugs* 75, 1935–1940
27. Anzalone, A.V. *et al.* (2020) Genome editing with CRISPR-Cas nucleases, base editors, transposases and prime editors. *Nat. Biotechnol.* 38, 824–844
28. Gao, C. (2021) Genome engineering for crop improvement and future agriculture. *Cell* 184, 1621–1635
29. Fischer, K. and Schnieke, A. (2023) How genome editing changed the world of large animal research. *Front. Genome Ed.* 5, 1272687
30. Whelan, A.I. and Lema, M.A. (2015) Regulatory framework for gene editing and other new breeding techniques (NBTs) in Argentina. *GM Crops Food* 6, 253–265
31. Hayes, B.J. and Daetwyler, H.D. (2019) 1000 bull genomes project to map simple and complex genetic traits in cattle: applications and outcomes. *Annu. Rev. Anim. Biosci.* 7, 89–102
32. Van Eenennaam, A.L. *et al.* (2019) Proposed U.S. regulation of gene-edited food animals is not fit for purpose. *NPJ Sci. Food* 3, 3
33. Kleppe, L. *et al.* (2022) Full production cycle performance of gene-edited, sterile Atlantic salmon - growth, smoltification, welfare indicators and fillet composition. *Aquaculture* 560, 738456
34. Hindar, K. *et al.* (2023) *Environmental Risk Assessment of Genetically Modified Sterile VIRGIN® Atlantic Salmon for Use in Research Trials in Aquaculture Sea-Cages*, Norwegian Scientific Committee for Food and Environment (VKM)
35. Ludlow, K. *et al.*, eds (2014) *Socio-economic Considerations in Biotechnology Regulation*, Springer
36. Kovak, E. *et al.* (2022) Genetically modified crops support climate change mitigation. *Trends Plant Sci.* 27, 627–629
37. Kathage, J. and Qaim, M. (2012) Economic impacts and impact dynamics of Bt (*Bacillus thuringiensis*) cotton in India. *Proc. Natl. Acad. Sci. U. S. A.* 109, 11652–11656

38. Shelton, A.M. *et al.* (2019) Bt Brinjal in Bangladesh: the first genetically engineered food crop in a developing country. *CSB Perspect. Biol.* 11, a034678
39. Areal, F.J. and Riesgo, L. (2022) *Sustainability of Bt Maize in Spain (1998-2021): An Economic, Social and Environmental Analysis*, Fundación Antama
40. Gusta, M. *et al.* (2011) Economic benefits of genetically-modified herbicide-tolerant canola for producers. *AgBioForum* 14, 1–13
41. Trigo, E. (2011) *Fifteen Years of Genetically Modified Crops in Argentine Agriculture*, ArgenBio
42. Hutchison, W.D. *et al.* (2010) Areawide suppression of European corn borer with Bt maize reaps savings to non-Bt maize growers. *Science* 330, 222–225
43. De Souza, A.P. *et al.* (2022) Soybean photosynthesis and crop yield are improved by accelerating recovery from photoprotection. *Science* 377, 851–854
44. Smyth, S.J. (2023) Sustainability in Canada and Europe: an assessment after 25 years of GM crop production. *ACS Agric. Sci. Technol.* 3, 1114–1116
45. Sutherland, C. *et al.* (2021) Correlating genetically modified crops, glyphosate use and increased carbon sequestration. *Sustainability* 13, 11679
46. Lunney, J.K. *et al.* (2016) Porcine reproductive and respiratory syndrome virus (PRRSV): pathogenesis and interaction with the immune system. *Annu. Rev. Anim. Biosci.* 4, 129–154
47. Cigan, M.A. and Knap, P.W. (2022) Technical considerations towards commercialization of porcine respiratory and reproductive syndrome (PRRS) virus resistant pigs. *CABI Agric. Biosci.* 3, 34
48. Burger, B.T. *et al.* (2024) Generation of a commercial-scale founder population of porcine reproductive and respiratory syndrome virus resistant pigs using CRISPR-Cas. *CRISPR J.* 7, 12–28
49. Cohen, J. (2024) Meat from gene-edited pigs could hit the market. *Science* 383, 940–941