The Science and Regulation of Food from Genetically Engineered Animals

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Introduction

Genetically engineered animals were first produced in the late 1970s.

Genetic engineering (GE) refers to the process of using recombinant DNA techniques to introduce new traits or alter the characteristics of an organism, or to enable the production of a useful biological substance such as a therapeutic protein. Genetically engineered animals were first produced in the late 1970s. Thirty years later many different species, including those traditionally consumed as food, have been produced, although most have not moved from the laboratory to commercialization. Genetically engineered animals are sometimes referred to as genetically modified (GM), living modified organism, transgenic, or bioengineered animals.

Genetically engineered animals can be divided into six broad classes (FDA 2009) based on the intended purpose of the genetic modification: (1) to enhance production attributes or food quality traits (e.g., faster growth); (2) to improve animal health (e.g., disease resistance); (3) to produce products intended for human therapeutic use (e.g., pharmaceutical products); (4) to enrich or enhance the animals' interactions with humans (e.g., new color varieties of pet fish); (5) to develop animal models for research purposes (e.g., pigs as models for cardiovascular diseases); and (6) to produce industrial or consumer products (e.g., fibers for multiple uses).

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Transgenic laboratory rodents such as mice and rats have become increasingly important for biological and biomedical research (Ireland et al. 2008). According to one estimate, 10 to 50 million GE laboratory animals are used annually in the United States (Mak 2008). Transgenic livestock have also been produced specifically as biomedical research models. In 2009, the first GE animal producing a pharmaceutical product, a goat synthesizing recombinant human

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In 2009, the first GE animal producing a pharmaceutical product was approved by the U.S. Food and Drug Administration.

antithrombin III in its milk, was approved by the U.S. Food and Drug Administration (FDA). This drug is an anticoagulant for the treatment of individuals with hereditary antithrombin deficiency, a blood-clotting disorder. To date, however, no GE animal intended for use as food by humans has received regulatory approval.

This paper describes how GE animals are currently regulated, outlines some criticisms of the current process, and discusses implications for the future of regulation of GE technology. A centerpiece of this paper is a case study of the attempt to gain regulatory approval of the AquAdvantage salmon.

How Genetically Engineered Animals Are Currently Regulated

To date, however, no GE animal intended for use as food by humans has received regulatory approval.

Some of the controversy regarding GE animals stems from issues of regulatory oversight of research, development, and postapproval marketing. The regulatory authority for overview of products from biotechnology (plants, animals, and microorganisms) was not established by a formal act of Congress. Rather, as biotechnology emerged in the mid-1980s, the White House Office of Science and Technology Policy promulgated the Coordinated Framework for the Regulation of Biotechnology (OSTP 1984, 1985, 1986), extending the scope of several existing laws to establish oversight of the production, field testing, and marketing of biotechnology products by federal agencies with authority under those laws. The Coordinated Framework did not specifically consider GE animals. Federal agencies then began rulemaking to implement the Coordinated Framework. The regulatory approach taken by the Coordinated Framework proved controversial, as did aspects of its implementation (Hallerman and Kapuscinski 1990; National Research Council 2000, 2002a,b).

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Genetically engineered animals are regulated under the new animal drug provisions of the federal Food, Drug, and Cosmetics Act (FD&C), leading to oversight by the FDA. The FDA considers the recombinant DNA (rDNA) construct to be a "new animal drug" under section 512 of the FD&C because it is "an article intended to alter the structure or function" of the animal. New animal drugs may be approved if they are shown to be safe and effective for the intended use. In a multistep scientific review process described by the FDA (2009), the agency examines the safety of the rDNA construct to the animal, the safety of food from the animal, and any environmental impacts posed (collectively the "safety" issues), as well as the extent to which the performance claims made for the animal are met ("efficacy").

Molecular characterization of the rDNA construct determines whether or not it contains DNA sequences from pathogens, toxins, viruses, or other organisms that could pose health risks to the GE animal or to those eating products from the animal. Molecular characterization of the GE animal lineage determines whether or not the rDNA construct is stably inherited over multiple generations. Phenotypic characterization assesses whether or not the GE animals are healthy, reach developmental milestones as non-GE animals do, and exhibit abnormalities. A durability assessment reviews the sponsor's plan to ensure that future GE animals of this line will be equivalent to those examined in the preapproval review.

If the GE animal is intended as a source of food, the FDA assesses whether or not the composition of edible tissues differs and whether or not its products pose more allergenicity risk than non-GE counterparts. The data requirements for demonstrating environmental safety of GE animals focus on the rDNA construct, host organism, production system, physical and biological confinement measures, and receiving environment.

If the GE animal is intended as a source of food, the FDA assesses whether or not the composition of edible tissues differs and whether or not its products pose more allergenicity risk than non-GE counterparts. To meet the requirements of the National Environmental Policy Act (NEPA), the FDA evaluates an environmental assessment of the GE animal and of conditions proposed for raising it. The data requirements for demonstrating environmental safety of GE animals focus on the rDNA construct, host organism, production system, physical and biological confinement measures, and receiving environment. Should the review indicate no significant impact on the environment under the proposed production conditions, the agency will publish a Finding of No Significant Impact (FONSI) along with an environmental assessment. A full environmental impact statement will be required if significant impact to humans or the natural environment is indicated.

Coordination with other federal agencies is through an informal consultative process. In the final step, the sponsors must support their claims for the GE animal—for example, that a growth hormone-transgenic salmon grows faster than non-GE counterparts or that an antithrombin III-transgenic goat produces the human antithrombin in its milk. Only with successful passage

through the multiple steps of the scientific review process would the FDA license commercial production of a GE animal. It is important to note that after approval is granted for an animal bearing an rDNA construct, that approval can be limited or revoked should adverse outcomes be observed, as is the case for animal or human drugs for which adverse outcomes are observed.

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Finally, the FDA has chosen to exercise "enforcement discretion" with regard to certain classes of GE animals, such as those of nonfood species that are raised and used in contained and controlled conditions or that pose minimal risk (FDA 2009). Examples include GE laboratory animals, including rodents used in research institutions, and "Glofish." The FDA, however, has reserved the right to take enforcement action if safety concerns associated with these GE animals are identified.

Oversight of GE animals by the FDA differs in certain key respects from oversight of GE plants by the U.S. Department of Agriculture (USDA), the FDA, and the Environmental Protection Agency (EPA) (reviewed by NRC 2000, 2002a,b). First, animals are regulated by one agency—the FDA. Genetically engineered plants are regulated by at least two and for specific applications, namely GE plants that express pesticides (called plant-incorporated protectants), by three agencies. The FDA's regulation for GE animals is based on mandatory premarket approval; its regulation for GE plants is based on voluntary premarket consultation. Another difference relates to the transparency of the regulatory process. The USDA publishes a public comment period in the *Federal Register* before each decision to grant "nonregulated status" of a crop. The proposed decision documents, which include the environmental assessment done pursuant to NEPA and their analysis of whether or not the crop is a plant pest, are also made publicly available. The same process is followed for crops grown under permit (e.g., pharmaceutical crops or GE trees) that have unique scientific issues or raise public concerns. The Freedom of Information Act (FOIA) also allows members of the general public to obtain copies of USDA Animal and Plant Health Inspection Service permit applications for moving or field testing GE plants, although confidential business information may be deleted from these copies.

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Before a GE plant expressing a plant-incorporated protectant is registered as a pesticide by the EPA, there is a notice in the *Federal Register* and an opportunity for public comment on the proposed decision by the agency. The EPA also makes all the information and data provided by the applicant available to the general public in a docket room. This release of information is in contrast to GE animal applications to the FDA, in which preapproval confidentiality is mandated unless the sponsor chooses to make the information public. This mandate is intended to protect the intellectual property and confidential business information of the company developing the product, although there is a requirement that a summary of data be made available if the product is approved. These confidentiality provisions are part of all "new animal drug" applications and are not uniquely associated with GE animals.

Criticisms of the Current Regulatory Process

From the viewpoint of diverse stakeholders, the FDA's regulatory approach has both strengths and weaknesses. Regarding strengths, premarket review of product safety and efficacy is rigorous and mandatory, and approval for marketing can be contingent on adhering to specified methods of containment and production known as "limitations for use." Agency approval of marketing is followed by monitoring, and approval for a product can be withdrawn if adverse outcomes are observed; critics note that the latter regulatory process can be long, which could prove problematic for a GE animal that could be reproducing in the environment.

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Regarding weaknesses, the regulatory process is not necessarily transparent. The existence and contents of an application for approval of a new animal drug are confidential; there may be many GE animal applications currently pending at the FDA but the FDA is prevented from acknowledging this by statute. From a superficial perspective, the FDA is therefore less transparent than the other agencies regulating GM plants. The business practice of those seeking regulatory approval from the FDA for products intended for human consumption, however, has been to seek prerelease of such information to avoid the appearance of secrecy to gain public acceptance. In an attempt to increase transparency, the FDA also declared its intention to hold public advisory committee meetings before the approval of any GE animal application for the foreseeable future (FDA 2009).

Regarding weaknesses, the regulatory process is not necessarily publicly transparent.

A second major criticism of the approval process is that although the FDA has legal authority to consider animal health and safety, it lacks authority to consider social concerns falling under the general heading of "ethics," including animal welfare considerations. The FDA requires that new animal drug applications include data about the health and safety of the GE animal. Some people are concerned about broader animal welfare considerations, such as the number of animals used to develop the GE line intended to enter commerce and abnormalities that may arise during the development. Other "ethical" concerns include fundamental moral objections to genetic engineering and even objections to the use of animals in general. Social concerns regarding animal welfare and ethics are not unique to GE animals; they have been expressed in conjunction with other animal-based technologies, including the use of animals in research, growth-enhancing technologies, cloning, and the introduction of recombinant bovine somatotropin. Although this is a major criticism of the new animal drug approval process, the criticism is usually not that these "ethical" issues should be addressed in the FDA safety approval process, but rather that they should be addressed somewhere by the federal government before an approval is granted.

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Another perceived problem is that the data required for regulatory review are produced by the corporation seeking approval for its product—not by the FDA or an independent body. This situation, however, is similar to the development of efficacy and safety data that is the responsibility of the applicant for all new animal and human drug applications. Shifting that regulatory requirement from the company interested in selling the product to the FDA would be a major departure from the current drug approval process and would effectively shift drug development responsibilities and the costs of regulatory compliance from the private to the public sector. Additionally it is not obvious how the agency could impartially evaluate data that had been generated in-house by the FDA.

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Perhaps the most often-expressed weakness of the FDA's regulatory approach is that there are no provisions dealing specifically with environmental risk. As noted earlier, a decision to approve a new animal drug constitutes a "federal agency action" under NEPA, requiring the development of an environmental assessment to consider the potential environmental impacts resulting from the action. The National Environmental Policy Act is procedural in nature, setting out how environmental impacts are considered but not how they will be managed. It does not give the FDA the authority to deny an application on environmental grounds. This act, however, does compel the agency to evaluate environmental impacts, and approval of a GE animal can be contingent on specified methods of containment and production to prevent negative environmental outcomes.

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Critics further contend that the FDA has limited expertise pertaining to environmental and fisheries issues. It should be noted, however, that the FDA is responsible for approving aquaculture drugs to treat fish disease. As such, the agency includes scientists with the appropriate expertise to ensure that aquaculture drugs are safe and effective and that treated food fish are safe for people and other animals to eat. Regarding the development of the GE fish, the FDA coordinates with the USDA, U.S. Fish and Wildlife Service, and National Marine Fisheries Service, agencies that some argue might be better placed to take the lead role in environmental risk assessment of GE fish. Proponents of the technology fear that because NEPA includes consideration of impacts to the poorly defined "human environment," which judges have variously considered to include economic, social, cultural, historic, and aesthetic harms, this environmental law is being co-opted by opponents to slow down or even obstruct the approval of GE products (Conko and Miller 2010).

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Finally, there is the equally contentious issue of food labeling. The principles of food labeling are the same for all foods—labels must be truthful and not misleading. The FDA cannot require that labels include information about production methods if there is no material difference in the products due solely to the production process. The National Research Council (NRC) (2002b) found that foods from GE animals, as a class, do not present different or greater safety concerns than their conventional counterparts. Nor has the FDA found that, as a class, GE animals differ materially in nutritional value, organoleptic properties, or functional characteristics. Therefore, the FDA does not consider the fact that a food was made using GE, in and of itself, to be a material difference. Voluntary labeling of all food is allowed if the label is neither false nor misleading.

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Case Study: The AquAdvantage Salmon

A formal application for an investigative new animal drug with intent to commercialize the AquAdvantage salmon (AA salmon) occurred on September 14, 1995, and more than 15 years later the application is still under regulatory review.

On August 25, 2010, the FDA announced its intention to hold a public Veterinary Medicine Advisory Committee (VMAC) meeting on the AA salmon in keeping with its commitment to hold public advisory committee meetings before the approval of any GE animal.

The AA salmon application included mitigation measures to abate environmental impacts by limiting the "product definition" to triploid, all-female, hemizygous transgenic Atlantic salmon produced at a single facility on Prince Edward Island (PEI) in Canada and grown out in a freshwater, land-based culture facility in Panama.

Environmental concerns remain a significant factor when considering the development of GE animals.

In a letter to the FDA dated April 26, 1993, AquaBounty Technologies (then A/F Protein) initiated discussions with the FDA seeking regulatory guidance for development and approval of a GE Atlantic salmon intended to grow faster than conventionally bred Atlantic salmon. Elliot Entis, then CEO of A/F Protein, noted (Entis, E. 2011. Personal communication) that this contact led to a number of meetings between A/F Protein and members of the A*gricultural Biotechnology Research Advisory Committee*, an interagency biotechnology committee organized by the USDA. Under the Coordinated Framework, the USDA was the lead agency to regulate GE plants, but there was no clear regulatory path for animals. The company petitioned for regulation under the FDA because they considered the rigorous pathway for approval would help assuage public concerns regarding food from GE animals. Additionally, the FDA new animal drug approval route has a defined endpoint, i.e., the product is either approved or it is not, rather than the more amorphous "no further questions" endpoint of GE plant food safety evaluations. A formal application for an investigative new animal drug with intent to commercialize the AquAdvantage salmon (AA salmon) occurred on September 14, 1995, and more than 15 years later the application is still under regulatory review.

On August 25, 2010, the FDA announced its intention to hold a public Veterinary Medicine Advisory Committee (VMAC) meeting on the AA salmon in keeping with its commitment to hold public advisory committee meetings before the approval of any GE animal (FDA 2009). Approximately two weeks before that meeting, the 172-page briefing package (containing a detailed summary of all the data and information related to the application and an 84-page environmental assessment) was simultaneously made available to the VMAC charged with providing scientific advice to the agency and to the general public (FDA 2010a). The information contained in the package included all the data and information that the agency reviewed as part of the application process, as well as the agency's evaluations. In the event that the AA salmon application receives approval, the briefing package will serve as the basis for the FOIA summary that normally accompanies new animal drug approvals. The FOIA summary will contain additional material such as the approved drug label, supplementary data on postmarket responsibilities, and other administrative information.

The AA salmon application included mitigation measures to abate environmental impacts by limiting the "product definition" to triploid, all-female, hemizygous transgenic Atlantic salmon produced at a single facility on Prince Edward Island (PEI) in Canada and grown out in a freshwater, land-based culture facility in Panama. Both locations were FDA-inspected and featured simultaneous, multiple, and redundant physical and geographical containment measures, effectively mitigating the impact of transgenic fish escape. And as an extra precaution, additional levels of biological containment were proposed, including the production of 100% female fish (unable to interbreed) and triploidy induction (results in sterility), with an average success rate of 99.8% (range 98.9 to 100%).

Environmental concerns remain a significant factor when considering the development of GE animals, as detailed in a report of the NRC (2002b), which was requested by the FDA after the AA salmon submission. The risk of harm from GE animals is the product of (1) harm given exposure to the hazard (i.e., the GE animal), and (2) probability of exposure (Muir 2004; Muir and Howard 2002, 2004). The probability of exposure in the case of the AA salmon was seen to be extremely small because of the triple redundancy of containment: (1) land-based production with physical confinement barriers (screens), (2) reproductive confinement measures resulting in 99% sterility and 100% female production stocks, and (3) thermally lethal lake and stream temperatures downstream from the proposed production facility in Panama.

Muir (Muir, W. M. Unpublished) reviewed AA salmon data collected by Moreau and colleagues (2010) quantifying critical life history characteristics, such as relative viability and mating success of AA salmon in multiple environments. Analysis of the data using the methodology detailed in Muir and Howard (2001) to determine the "net fitness" of AA salmon showed that none of the net fitness components were enhanced by expression of the transgene. As a result, the "Trojan gene effect" (Muir and Howard 1999) would not be predicted to occur in the unlikely event that AA salmon did escape from confinement. Rather, selection over time would be expected to simply purge the transgene from any established population, suggesting a low probability of harm resulting from exposure to AA salmon (i.e., the hazard).

The unanimous conclusion of the FDA scientists after examining all of the data and information summarized in the AA salmon briefing packet was that the food from AA salmon "is as safe as food from conventional Atlantic salmon, and that there is a reasonable certainty of no harm from the consumption of food from this animal"; in addition, there "is substantial, reliable information available in the environmental assessment document" to conclude that GE AA salmon "are not expected to have a significant impact on the quality of the human environment (1) in the United States; (2) in foreign nations not involved in the action; or (3) on the global commons when raised and reared under the current conditions of physical, biological, and geographic/geophysical containment present at hatchery and grow-out facilities in Canada and Panama" (FDA 2010a).

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Likewise, the VMAC charged with providing advice and recommendations to the agency found (1) "no evidence in the data to conclude that the introduction of the construct was unsafe to the animal," (2) that the studies selected to evaluate whether or not there was a reasonable certainty of no harm from consumption of foods derived from AquAdvantage salmon were "overall appropriate and a large number of test results established similarities and equivalence between AquAdvantage Salmon and Atlantic salmon," and (3) that the AA salmon did grow faster than their conventional counterparts. As to whether or not any potential environmental impacts from AA salmon production were adequately mitigated by the proposed conditions of use, the committee concluded that although they "recognized that the risk of escape from either facility could never be zero, the multiple barriers to escape at both the PEI and Panama facilities were extensive" (FDA 2010b).

The regulatory process for the AA salmon was significantly more transparent and participatory than what has occurred for other animal drugs.

Less than two weeks after the public meeting that was intended to increase transparency, clarity, and public confidence in the GE animal regulatory process, two separate letters from 11 senators and 29 members of Congress were sent to the FDA commissioner identifying a multitude of problems with the FDA's GE animal regulatory process, specifically citing the lack of transparency and opportunity for public participation. It should be recognized, however, that in the case of the AA salmon application, AquaBounty has maintained a public website detailing their intent to commercialize AA salmon for a number of years. The FDA obtained permission from the sponsor to make all of the data and information in the VMAC briefing packet publicly available before the meeting and provided an opportunity for public participation through an oral comment period during the VMAC meeting. As such, the regulatory process for the AA salmon was significantly more transparent and participatory than what has occurred for other animal drugs. In February 2011, two senators from Alaska reintroduced a bill that would ban GE salmon entirely.

As of April 2011, the FDA had not yet made a decision regarding the environmental review of the AA salmon.

As of April 2011, the FDA had not yet made a decision as to whether or not to make a FONSI determination regarding the environmental review of the AA salmon under the proposed "Limitations for Use" or whether or not it will require the preparation of a full environmental impact statement (EIS). It should again be noted that NEPA is procedural in that it requires agencies to assess the environmental impacts of their "actions" and then work with the sponsor to mitigate any potential impacts. In the case of the AA salmon, such mitigations include genetic, biological, and physical containment. A final decision to prepare a FONSI or an EIS for the AA salmon application will be made after comments from the public and appropriate experts have been received and evaluated by the agency.

Implications for the Future of Regulation and the Technology

All technologies are associated with some form of risk, but a critical and often-overlooked issue is that all risks are relative to alternatives.

All technologies are associated with some form of risk, but a critical and often-overlooked issue is that all risks are relative to alternatives. Harvest of wild fish depletes oceanic stocks and does not present a long-term, ecologically sustainable solution to rising global demand for fisheries products. Selection for fast-growing fish using conventional breeding results in a shift in the allele frequencies of many growth-associated genes. Even fish selectively bred for fast growth differ at many loci from wild populations. Farmed fish are known to have a fitness disadvantage, called a genetic load, in natural environments because domestication genes are only favorable in domestic environments (Lynch and O'Hely 2001). It is known that matings between escaped farmed salmon and wild native fish result in a "substantial risk of extinction for natural populations" (Lynch and O'Hely 2001). Thus, the comparative risk of sterile transgenic AA salmon is likely to be less than that of fertile, selectively bred Atlantic salmon.

Subjecting conventionally bred and GE animals to different regulatory standards in the absence of unique risks is inconsistent from a scientific perspective.

Forgoing access to GE technology may jeopardize future access to improved genetic lines resulting from new technological developments.

The current regulatory approach, coupled with the prolonged and unpredictable time frame, has resulted in an inhibitory effect on commercial investment in the development of GE animals for agricultural applications with ramifications for U.S. agriculture and food security.

The current regulatory process associated with GE animals focuses on potential risks associated with GE animals, with little consideration of counterbalancing benefits (Murray and Maga 2009) or positive environmental impacts. Paradoxically, similar risks known to be engendered by conventionally bred animals (e.g., fish selected to grow faster, outcompeting wild stocks) undergo no regulatory approval; only GE animals trigger an extensive premarket review and NEPA review requirement. Subjecting conventionally bred and GE animals to different regulatory standards in the absence of unique risks is inconsistent from a scientific perspective.

The protracted evaluation of the AA salmon and continuing uncertainties in the regulatory process and time line have essentially halted commercial and public investment in the development of GE animals for agricultural applications in the United States, although transgenic animal agricultural research is ongoing in other countries. This outcome has long-term implications for the competitiveness of U.S. agriculture and the future geographic location of GE animal research, development, and production. Forgoing access to GE technology may jeopardize future access to improved genetic lines resulting from new technological developments (e.g., disease-resistant GE animals [Lyall et al. 2011]), with implications on food security and other broadly supported societal goals (e.g., improved animal welfare and human health).

Conclusions

The regulatory process associated with GE animals for food production currently employs the new animal drug provisions of the federal Food, Drug, and Cosmetics Act and considerations from the National Environmental Policy Act. Although the current regulatory approach includes a multistep hierarchical risk-based strategy to assess GE animals and their edible products, critics argue that the process is flawed for a number of reasons. Some contend it is not sufficiently rigorous, others that it does not adequately address environmental risks and lacks both transparency and public participation. To date, no applications for GE animals intended as a source of food have been approved, although a fast-growing GE salmon (AquAdvantage salmon) application was the subject of public FDA hearings in September 2010. The FDA's evaluation concluded that the GE salmon were as safe to eat as food from conventional Atlantic salmon, and that the GE salmon were not expected to have a significant environmental impact when raised and reared with the multiple physical, biological, and geographic/geophysical containment measures detailed in the application.

Despite the FDA's attempts to increase transparency and public participation in the regulatory process**,** opposition to the GE salmon from environmental and consumer groups, food safety advocates, and commercial and recreational fisheries associations remains. The current regulatory approach, coupled with the prolonged and unpredictable time frame, has resulted in an inhibitory effect on commercial investment in the development of GE animals for agricultural applications with ramifications for U.S. agriculture and food security.

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