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THE NEXT FRONTIER IN FOOD: FDA REGULATION OF  
GENETICALLY ENGINEERED ANIMALS

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## **THE NEXT FRONTIER IN FOOD: FDA REGULATION OF GENETICALLY ENGINEERED ANIMALS**

### **ABSTRACT**

Genetically engineered (GE) animals designed for human use, whether to be eaten as food, to produce drugs, or to be enjoyed as pets, carry the potential for enormous benefits and enormous harm. Currently, the Food and Drug Administration's (FDA) 2009 Final Guidance on GE animals demonstrates that agency believes it may regulate all GE animals regardless of their use under its authority to regulate new animal drugs (NADs), but that it will selectively use its enforcement discretion over only some categories of those animals (primarily those intended for food or to producer drugs). It has also taken the position that the GE nature of an animal for food in itself does not necessitate labeling of the food product, the same position it took for GE crops. In the last few years, it has declined to regulate a GE fish intended for use as a pet, has approved a new animal drug application (NADA) for a GE goat intended to produce a human drug, and is currently considering approval of a GE fish intended to be marketed as food. An examination of these examples demonstrates that the 2009 Guidance is flawed in its approach and underlying assumptions, and that the use of the NAD scheme to regulate this fundamentally new type of animal is inappropriate. FDA's approach thus far results in insufficient and opaque inquiries into the safety of the GE animal to humans, the animal, and the environment, and vests too much power in the agency's discretion, rendering its decisions effectively judicially unreviewable. The best solution to this problem would be for Congress to institute a comprehensive statutory and regulatory scheme to govern GE animals, giving FDA authorization to regulate GE animals in a way more tailored to the unique issues they present, vesting in the Environmental Protection Agency authorization to conduct the relevant environmental inquiries, and mandating the labeling of food from GE animals. Such an approach would be more in line with the underlying science of GE, and would restore public trust in FDA's assurances of the safety of their food and drugs.

If the salmon you were about to buy for dinner tonight were engineered with a gene from another fish cut and pasted into it, but was cheaper than other salmon, would you still buy it? What if the salmon you ate for dinner last night was genetically engineered that way, and you never knew it? The Food and Drug Administration (FDA) is currently reviewing an application for the marketing of AquAdvantage Salmon – which has been genetically engineered (GE) to grow to full size twice as fast as normal salmon – and would be the first GE animal approved for human consumption. FDA does not currently intend to require the fish to be labeled as GE to the consumer. In recent years, there has been a revolution in the genetic engineering of animals for human benefit, and FDA has scrambled to devise a scheme with which to regulate them. Its response was to utilize an old but familiar regulatory framework designed for an entirely different purpose. This has resulted in an incoherent policy that is out of tune with the realities of the unique risks GE animal products pose to humans, animals, and the environment, and with consumers' overwhelming interest in knowing what exactly they are eating.

Part I of this paper will provide a background on the science of genetic engineering of organisms. Part II will describe the current regulatory framework through which FDA and other agencies regulate GE organisms, focusing on animals and those used as food. Part III will examine three recent examples of FDA's regulation of GE animals to shed light on how the regulatory scheme works in practice. Part IV will present conclusions on the extent to which the recent cases demonstrate problems with the current regulatory scheme, and suggest possible remedies to improve and streamline regulatory oversight of GE animals.

## **I. HISTORY AND BACKGROUND OF GENETICALLY ENGINEERED FOOD**

### **A. Scientific Background**

Humans have conducted genetic modification of animals and plants, in a formal sense,

since organisms with desirable traits were first bred together – crossbreeding of different species of animals dates back to the mule.<sup>1</sup> Since the 1970s, however, humans have also gained the ability to genetically engineer an organism by inserting of a gene from one organism into the deoxyribonucleic acid (DNA) of another of the same or different species, what is referred to as recombinant DNA (rDNA).<sup>2</sup> In the rDNA technique, first, a desirable trait from a donor animal is determined. Then, the gene which codes for that trait is identified, isolated, and copied. That isolated gene (now a “transgene”) is “pasted” into the DNA of an animal cell at or around its embryo stage.<sup>3</sup> As the animal develops, it will express the new trait (now a “transgenic” animal), and transgenic animals can then be bred with one another in traditional ways to create a line of animals expressing the transgene. Because DNA and its translation into proteins is common to all living things, a gene from any organism is able to be transferred to any other; i.e., an animal could be engineered to express a trait from another animal, a plant, a bacterium, etc.

With similar techniques, scientists have genetically engineered plants for human consumption. The first commercial GE food was the Flavr Savr tomato, introduced in 1994, which was modified to ripen more slowly on the vine.<sup>4</sup> Since then, over 60 GE plants have been

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<sup>1</sup> RACHEL BORGATTI & EUGENE H. BUCK, U.S. CONG. RES. SERV., RS21996, GENETICALLY ENGINEERED FISH AND SEAFOOD 1 (Dec. 2004).

<sup>2</sup> U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-02-566, GENETICALLY MODIFIED FOODS: EXPERTS VIEW REGIMEN OF SAFETY TESTS AS ADEQUATE, BUT FDA'S EVALUATION PROCESS COULD BE ENHANCED 4 (May 2002) [hereinafter GAO 02-566]. Such organisms are commonly alternatively referred to as “genetically engineered” and “genetically modified.” Although in this article I am formally referring to only genetic modification through heritable rDNA constructs, for the sake of consistency and convenience, I will use the term “genetically engineered”/ “GE” to describe products of that process.

<sup>3</sup> U. N. FOOD AND AGRI. ORG., CODEX ALIMENTARIUS COMM'N, GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS DERIVED FROM RECOMBINANT-DNA PLANTS, CAC/GL 45-2003 1 (2008), *available at* [http://www.codexalimentarius.net/download/standards/10021/CXG\\_045e.pdf](http://www.codexalimentarius.net/download/standards/10021/CXG_045e.pdf) [hereinafter CODEX ALIMENTARIUS]. There are in actuality a variety of mechanisms by which the new DNA material is inserted into the host animal's DNA, such as microinjection, use of bacterial or viral vectors, etc. Also, insertion can occur around the gamete stage or around the embryonic stage.

<sup>4</sup> Gregory N. Mandel, *Gaps, Inexperience, Inconsistencies, and Overlaps: Crisis in the Regulation of Genetically Modified Plants and Animals*, 45 WM. & MARY L. REV. 2167, 2176 (Apr. 2004).

developed and sold as food.<sup>5</sup> Most of these modifications were to agricultural properties of the plant, such as increased resistance to pesticides or insect attacks, but some have been engineered for nutritional purposes, such as modified oil in a soybean.<sup>6</sup>

### **B. Risks and Benefits of GE Foods**

Following from the infinite number of ways in which living things can be genetically recombined, GE foods have enormous potential for human benefits. One obvious benefit is increased food production, whether by making an organism less vulnerable to outside threats from viruses, drought, or weeds, or by creating an animal which reaches full growth earlier, saving costs in rearing it.<sup>7</sup> Genetic engineering can also be used to promote human health by increasing the quality and nutrition of food in any variety of ways; this type of engineering has been touted the “next generation” of GE foods.<sup>8</sup> Also, of great importance to FDA, organisms can be engineered to produce proteins or hormones humans can use as drugs, where the organism can produce a certain chemical more efficiently than a synthetic process. GE foods also can carry environmental benefits: e.g., plants that are engineered to produce their own pesticides reduce the need for spraying,<sup>9</sup> and pigs that have been engineered to produce less phosphate in their manure.<sup>10</sup> These are just a few examples of the enormous benefits genetic engineering could have to increase and improve the world’s supply of food.

Despite its benefits, genetic engineering is not without its risks. Scientists are still beginning to understand the complexity with which genes interact with one another. “Unintended effects can result from the random insertion of DNA sequences into the animal genome, which

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<sup>5</sup> GAO 02-566, *supra* note 2, at 9.

<sup>6</sup> *Id.*

<sup>7</sup> *Id.* at 8.

<sup>8</sup> Mandel, *supra* note 4, at 2179.

<sup>9</sup> *Id.* at 2185.

<sup>10</sup> S.P. Goloban et al., *Pigs expressing salivary phytase produce low-phosphorous manure*. 19 NATURE BIOTECH. 741-45 (2001).

may cause disruption or silencing of existing genes, activation of silent genes, or modifications in the expression of existing genes. Unintended effects may also result in the formation of new or changed patterns of metabolites.”<sup>11</sup> These unintended effects can create three main different types of risks: risks to the safety of the food derived from the GE for human consumption, to the environment, and to the animal itself.

The main human health risks include increased toxicity, allergenicity, and horizontal gene transfers.<sup>12</sup> In the first two examples, the GE organism has altered properties itself that render it more toxic or allergenic to humans. With horizontal gene transfers, the gene travels from the GE animal to another organism, most commonly bacteria. Thus, GE organisms used as food carry the particular risk of having their properties transferred to the bacteria that live in the human digestive tract, in ways harmful to human health.<sup>13</sup>

GE organisms also carry environmental risks. In crops, gene transfer can occur by GE plants cross-pollinating other plants, converting non-traditional weeds into weeds, or horizontally through bacteria or viruses.<sup>14</sup> GE animals carry the risk of physical escape into the environment, harming wild animals by increased competition or predation and upsetting the ecosystem.<sup>15</sup> Some studies have forwarded a “Trojan gene hypothesis”, whereby a GE fish was found to outcompete non-altered fish for mates, but rendered less fit offspring, eventually resulting in the demise of the wild population.<sup>16</sup>

Finally, genetic engineering can prove harmful to the animal itself, with negative consequences to animal anatomy, such as physical deformity, and to behavior, such as reduced

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<sup>11</sup> CODEX ALIMENTARIUS, *supra* note 3, at 2.

<sup>12</sup> Le Curieux-Belfond et al., *Factors to consider before production and commercialization of aquatic genetically modified organisms: the case of transgenic salmon*, 12 ENVIRONMENTAL SCIENCE & POL’Y 174-75.

<sup>13</sup> *Id.* at 175.

<sup>14</sup> NAT’L RES. COUNCIL, ENVIRONMENTAL EFFECTS OF TRANSGENIC PLANTS: THE SCOPE AND ADEQUACY OF REGULATION 66-67 (2002).

<sup>15</sup> Borgatti & Buck, *supra* note 1, at 4.

<sup>16</sup> *Id.*

reproductive behavior.<sup>17</sup> This raises additional ethical concerns, as well as concerns for the safety of the food derived from the animal.

## II. FDA REGULATION OF FOOD FROM GE PLANTS

Despite these risks, FDA (and the federal government in general) has generally taken a stance that GE organisms used for food have substantial equivalence to their original counterparts, and thus they carry no unique risks. This view was first expressed implicitly in the 1986 Coordinated Framework for Regulation of Biotechnology promulgated by the White House Office of Science and Technology Policy, which articulated that GE products would be regulated by FDA, EPA, and USDA under already-existing statutes and regulations.<sup>18</sup> “The foundation for this decision was a determination that the process of biotechnology was not inherently risky, and therefore, that only the products of biotechnology, not the process itself, required oversight.”<sup>19</sup>

### A. Applicable Statutory Framework

Following suit, FDA was thus faced with the choice to regulate food from GE plants either under the adulteration clause of the Food, Drug, & Cosmetic Act (FDCA) §402, which governs food that “bears or contains any deleterious substance which may render it injurious to health”,<sup>20</sup> or under the food additives clause §409, which governs substances intended for use in food, that may reasonably be expected to become a component in food, or that otherwise may affect the characteristics of food.<sup>21</sup> The two provisions differ primarily in the degree of FDA approval required before the food can be sold. Under §409, the producer of a food additive must

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<sup>17</sup> Mendal, *supra* note 4, at 2202.

<sup>18</sup> Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302, 23,302-3 (June 26, 1986). “The manufacture by the newer technologies of food, the development of new drugs, medical devices, biologics for humans and animals, and pesticides, will be reviewed by FDA, USDA and EPA in essentially the same manner for safety and efficacy as products obtained by other techniques. The new products that will be brought to market will generally fit within these agencies' review and approval regimens.” *Id.* at 23,302.

<sup>19</sup> Mendal, *supra* note 4, at 2216.

<sup>20</sup> 21 U.S.C.A. §402(a)(1) (2010).

<sup>21</sup> 21 U.S.C.A. §409 (2010).



file with FDA a “food additive petition” before marketing, which requires that the producer perform extensive safety testing to demonstrate there is no “reasonable certainty of harm” from the additive.<sup>22</sup> If FDA is satisfied of this, it then issues a letter stating that the food additive has been approved. The exception for this rigid premarket approval process for food additives is if the additive is generally regarded as safe (GRAS) – the GRAS determination was intended to cover traditional spices and vinegar, e.g.<sup>23</sup> In contrast, the §401 adulteration clause requires no premarket approval and “generally relies upon good manufacturing practices and post-marketing detection and recall authority to protect public health.”<sup>24</sup>

With regard to the labeling of all food ingredients, a food is “misbranded” if it is “false or misleading in a material respect”,<sup>25</sup> or “fails to reveal facts material in light of such representations or material with respect to consequences which may result from the use of the article.”<sup>26</sup> Moreover, food additives must be listed on the ingredients section of the food label.<sup>27</sup>

### **B. Splitting the Difference: the 1992 Policy on GE Plants**

In its 1992 *Statement of Policy: Foods Derived from New Plant Varieties* (“1992 Policy”) FDA charted the middle ground: it determined to primarily regulate GE foods under the §401 adulteration clause, but in an “amplified” way.<sup>28</sup> It determined that GE foods would be ordinarily considered GRAS because “[i]n most cases, the substances expected to become components of food as a result of genetic modification of a plant will be the same as or substantially similar to

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<sup>22</sup> *Id.*

<sup>23</sup> David L. Pelletier, *Science, Law, and Politics in the Food and Drug Administration’s Genetically Engineered Foods Policy: FDA’s 1992 Policy Statement*, 63 NUTRITION REVS. 171, 173 (May 2005).

<sup>24</sup> *Id.* at 173.

<sup>25</sup> 21 U.S.C.A. §343(a) (2010).

<sup>26</sup> 21 U.S.C.A. §321(n) (2009).

<sup>27</sup> Pelletier, *supra* note 23, at 173.

<sup>28</sup> *Id.*; *Statement of Policy: Foods Derived from New Plant Varieties*, 57 Fed. Reg. 22,94-85 [hereinafter 1992 Policy].

substances commonly found in food, such as proteins, fats and oils, and carbohydrates.”<sup>29</sup>

Following this was the related proposition that the presence of the rDNA was not *itself* a food additive, but rather that proteins coded and produced by the rDNA would be food additives, if they altered the nutritional profile of the food.<sup>30</sup> Importantly, the manufacturer and not FDA makes this GRAS determination.<sup>31</sup>

This policy was founded on one major assumption: that “rDNA techniques are simply an extension of genetic modification that has been used by humans for thousands of years, that it creates no fundamentally new risks, and that it is more precise and predictable than traditional plant breeding.”<sup>32</sup> Additionally, its determination not to conduct stringent pre-market review of the safety of GE foods stemmed from the scientific difficulty of proving any unintended consequences of GE crops.<sup>33</sup>

Instead, the 1992 Policy described a voluntary process by which a producer would follow a set of decision trees provided by FDA to guide it in its GRAS determination, would consult with FDA throughout the process, and if successful, receive a letter from FDA that reiterated the conclusions the developer had drawn and stated “FDA has no further questions.”<sup>34</sup> Although the pre-market cooperation with FDA was made voluntary, according to FDA, producers have nonetheless sought such consultation before marketing every new variety of GE food to date.<sup>35</sup> Finally, FDA determined that GE foods did not have to be labeled as such, as the

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<sup>29</sup> *Id.*

<sup>30</sup> *See id.* at 22,900. “Nucleic acids are present in the cells of every living organism, including every plant and animal used for food by humans or animals, and do not raise a safety concern as a component of food.” In contrast, “the intended expression product in a food could be a protein, carbohydrate, fat or oil, or other substance that differs significantly in structure, function, or composition from substances found currently in food. Such substances may not be GRAS and may require regulation as a food additive.” *Id.*

<sup>31</sup> *Id.* at 22,989.

<sup>32</sup> Pelletier, *supra* note 23, at 176.

<sup>33</sup> *Id.* at 173.

<sup>34</sup> *Id.* at 173-74.

<sup>35</sup> *Id.* at 175.

use of rDNA was not a “material fact”, but would require labeling only if the food differed from its counterpart in its nutritional profile.<sup>36</sup>

The 1992 Policy also addressed FDA’s potential obligations under the National Environmental Protection Act (NEPA). Under NEPA, “[f]or major federal actions, agencies must either prepare an EIS [Environmental Impact Statement] examining the environmental impact of the proposed action, prepare an EA [Environmental Assessment] determining whether or not to prepare an EIS, or claim that the action falls within a Categorical Exclusion.<sup>37</sup> The 1992 Policy noted that while food additive permits would constitute major action for NEPA purposes, FDA did not consider any actions “other than the promulgation of food additive regulations . . . [to] constitute agency action under NEPA”.<sup>38</sup> Because FDA chose primarily *not* to regulate GE foods as a food additive, it thus effectively exempted almost all GE plant foods from NEPA review.

### **C. Challenge to the 1992 Policy: *Alliance for Bio-Integrity v. Shalala***

While opponents to the 1992 Policy challenged it in federal courts, judges stood behind FDA’s determinations. In *Alliance for Bio-Integrity v. Shalala*,<sup>39</sup> plaintiffs representing concerned scientists and others launched four main attacks on the guidance: (1) it was invalid because it had not been subjected to notice and comment proceedings under the Administrative Procedure Act (APA), 5 U.S.C. §553, (2) FDA did not comply with NEPA by completing EA or an EIS in the issuance of the policy, (3) FDA’s presumption that rDNA foods are GRAS and therefore do not require food additive petitions under §321 was arbitrary and capricious, and (4) FDA’s decision not to require labeling for rDNA-developed foods was arbitrary and capricious

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<sup>36</sup> 1992 Policy, *supra* note 28, at 22,991.

<sup>37</sup> *Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166, 174 (D.D.C. 2000); *see* 42 U.S.C. § 4321 *et seq.*

<sup>38</sup> 1992 Policy, *supra* note 28, at 23,004.

<sup>39</sup> 116 F. Supp. 2d 166.

because it did not consider widespread consumer interest in the labeling of GE foods.<sup>40</sup>

The court dismissed the claims and found for FDA, first holding that (1) the guidance was a “statement of policy” and thus did not require formal notice and comment proceedings under the APA because it was not intended to be binding upon the industry or FDA. It found that the guidance only created a *presumption* that rDNA foods were GRAS, which left the agency freedom to exercise discretion if it wished to make an individual determination that a particular rDNA food was not GRAS.<sup>41</sup> It also held that (2) FDA did not violate NEPA by failing to conduct an EA or EIS because the guidance was not a “major federal action” in the meaning of NEPA,<sup>42</sup> because it was reversible, maintained the substantive status quo for regulation of rDNA foods, and took no overt action.<sup>43</sup> The court granted *Chevron* deference to FDA’s interpretation of FDCA §321 that rendered rDNA foods presumptively GRAS to find (3) that the agency’s determination was not arbitrary and capricious.<sup>44</sup> Finally, it also granted *Chevron* deference to the agency’s interpretation of “material” difference under §321(n) – that the use of rDNA itself did not constitute a material difference and that consumer demand alone did not impose a labeling requirement – to conclude that FDA’s decision not to require the labeling of rDNA foods was not arbitrary and capricious.<sup>45</sup> Thus, the case allowed FDA wide discretion to regulate food from GE plants as it wished, shielded by the double protections of “statement of policy” and *Chevron* deference.<sup>46</sup>

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<sup>40</sup> *Id.* at 170. Plaintiffs also challenged that the Guidance (5) violated the Free Exercise Clause and (6) violated the Religious Freedom Restoration Act, *id.*, but those challenges are beyond the scope of this paper.

<sup>41</sup> *Id.* at 172-73.

<sup>42</sup> 42 U.S.C. § 4332(2)(c)(i) (2010).

<sup>43</sup> *Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d. at 175.

<sup>44</sup> *Id.* at 176-77.

<sup>45</sup> *Id.* at 178.

<sup>46</sup> An FDA decision not to require labeling was also upheld in *Stauber v. Shalala*, 895 F. Supp. 1178 (W.D. Wis. 1995), in which the agency’s determination not to require labeling milk from recombinant bovine somatotrophin (rbST)-treated cows was granted *Chevron* deference and found not to be arbitrary and capricious.

### III. FDA REGULATION OF GE ANIMALS

On the heels of genetically engineering plants for commercial use came the genetic engineering of animals. The first GE animals were mice produced in the early 1980s.<sup>47</sup> GE animals are currently being developed for a variety of direct human uses: to be consumed as human food, to produce drugs used by humans, and as human pets. Additionally, they are used in research laboratories around the country. As in 1992 with plants, FDA was forced to devise a method of regulating food and drugs produced by such animals, to determine which authorizing statutes to employ, and to decide whether to make its determinations binding or flexible. FDA has chosen to regulate GE animals in a manner that in one sense conforms with the 1992 Policy view that genetic engineering itself does not inherently render the food product unsafe, resulting in the use of an existing framework to regulate the product, and yet still laid out a much more rigorous, premarket approval process for food products from GE animals.

#### A. 2009 Guidance on GE Animals

##### 1. Regulated Article: GE Animals Contain New Animal Drugs

In 2008, FDA issued a proposed draft guidance on the regulation of GE animals. After 60 days of comments from the industry, FDA issued a final guidance with essentially the same provisions, *Guidance for Industry: Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs* (“2009 Guidance”).<sup>48</sup> The hallmark of the 2009 Guidance is that it asserted FDA’s authority over *all* GE animals (regardless of their ultimate use) through its FDCA authority over “new animal drugs” (NADs).<sup>49</sup> §201(g) defines a “new

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<sup>47</sup> FDA Center for Veterinary Medicine, *Guidance for Industry 187: Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs* (Jan. 15, 2009), *available at* <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf> [hereinafter 2009 Guidance].

<sup>48</sup> *Id.*

<sup>49</sup> 21 U.S.C.A. § 201; 2009 Guidance, *supra* note 47, at 4-5.

animal drug” as any “article[] (other than food) intended to affect the structure or function of . . . animals.”<sup>50</sup> FDA determined that an rDNA construct is an animal drug because its insertion into the animal’s genome alters the animal’s structure or function, which therefore grants FDA authority over the resulting GE animal and its progeny.<sup>51</sup>

Under the statute, NADs are generally deemed unsafe unless FDA has approved a new animal drug application (NADA) for the particular use of the drug, except for the case of certain Investigational New Animal Drugs (INADs).<sup>52</sup> Because each transformation event is unique, i.e., because the rDNA cannot be precisely placed in a certain portion of the genome and thus likely ends up at a different site each time, a NADA would only cover the animal with the rDNA at a particular genomic locus. Yet because the guidance limited its purview to heritable rDNA constructs, each NADA will also cover all animals containing the same rDNA construct derived from the same transformation event, such as offspring descended from the original transgenic animal as a result of breeding.<sup>53</sup>

## 2. Enforcement Discretion

Although the 2009 Guidance asserted FDA’s authority to regulate *all* GE animals, it was clear that in most cases FDA would not intend to regulate (1) GE animals of non-food species regulated by other government agencies or entities, such as insects developed for pest control, and (2) GE laboratory animals of non-food species used for experimentation in research institutions.<sup>54</sup> Thus, similar to the 1992 Policy, FDA left itself a wide amount of leeway as to which products it would actually enforce.

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<sup>50</sup> 2009 Guidance, *supra* note 47, at 4.

<sup>51</sup> *Id.*

<sup>52</sup> 21 U.S.C.A. §§ 360(a)(1), 360(a)(3).

<sup>53</sup> 2009 Guidance, *supra* note 47, at 6.

<sup>54</sup> *Id.*

### 3. Labeling

Also similar to the 1992 Policy, the 2009 Guidance states that food derived from GE animals will *not* ordinarily need to be labeled, citing the same presumption that rDNA food is not different in a “material” way from its non-GE counterpart.<sup>55</sup> Similarly, it stated that if the nutritional profile of the GE food differed from its non-GE counterpart, this information would be required to be revealed in labeling.<sup>56</sup>

### 4. Environmental Review

In compliance with NEPA, a NADA must either include a claim for a categorical exclusion or an EA.<sup>57</sup> “The EA is a public document that provides sufficient information to allow FDA to either prepare an environmental impact statement (EIS) or issue a finding of no significant impact (FONSI).”<sup>58</sup> The 2009 Guidance also acknowledges the fact that the content of the EA will vary greatly with the organism and intended use of the GE product, and recommends that producers contact and work closely with FDA before the preparation of the EA.<sup>59</sup> The EA becomes public when the animal is approved.<sup>60</sup> The guidance also recognized that the EPA may also assert jurisdiction over certain GE animals, such as insects, and that FDA was discussing with it “the best approach for oversight.”<sup>61</sup>

### 5. Application

The guidance lays out a detailed process for obtaining approval for a GE animal NAD. It notes that this is a “recommended process” on top of those required by existing NAD

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<sup>55</sup> *Id.* at 14.

<sup>56</sup> *Id.* at 14.

<sup>57</sup> 21 C.F.R. §514.1(b)(14).

<sup>58</sup> 2009 Guidance, *supra* note 47, at 18.

<sup>59</sup> *Id.* at 18.

<sup>60</sup> *Id.*

<sup>61</sup> *Id.* at 5, fn. 1.

regulations, which includes seven steps.<sup>62</sup> The Center for Veterinary Medicine (CVM) will then consider together the safety of the rDNA construct to the animal, the safety of the food produced by the animal, and the environmental impact, if any, of the animal. The guidance also describes the producer's post-approval responsibilities for a NAD, already required under existing statutes and regulations,<sup>63</sup> including registration and drug listing, recordkeeping, filing supplements, and periodic reporting.<sup>64</sup> In terms of publicity, it stated that "at present" FDA intends to hold public Veterinary Medicine Advisory Committee (VMAC) meetings prior to approving any GE animal, but that it "may revisit that policy in the future."<sup>65</sup>

## 5. Conclusions

The 2009 Guidance is similar to the 1992 Policy in that FDA chose to regulate GE foods through non-binding recommendations that leave many determinations to agency discretion, rather than through notice-and-comment rulemaking. It also reached the same determination not to label GE food as such. However, FDA clearly recognized the increased potential for danger from food from GE animals by describing a much more stringent mechanism to regulate their products long before they ever reach the shelves (by using the regulatory scheme for NADs), in stark contrast to the lax standard for products from GE plants that investigates whether or not the food produced is adulterated.

### **B. Comments and Criticism of the 2009 Guidance**

Like its counterpart almost two decades prior, the 2009 Guidance was not without its

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<sup>62</sup> *Id.* at 19-24. Step 1 is product identification; Step 2 is molecular characterization of the construct; Step 4 is phenotypic characterization of the GE animal; Step 5 is a genotypic and phenotypic durability assessment; Step 6 is the food/feed safety and environmental safety assessments; Step 7 is effectiveness/claim validation. *Id.*

<sup>63</sup> 21 U.S.C. §§ 360, 356(a); 21 C.F.R. §§ 514.8, 514.80 (2008).

<sup>64</sup> 2009 Guidance, *supra* note 47, at 24-26.

<sup>65</sup> *Id.* at 12.



critics. The most thorough comments to the proposed draft, submitted by the Consumers Union (“CU Comments”), contained four main criticisms of the guidance.<sup>66</sup>

The first concern is that the guidance is not legally binding, and so producers are theoretically free to deviate from it as they see fit. Second is the lack of transparency in the NADA process.<sup>67</sup> Under the 2009 Guidance, almost all of the application process can take place without notification to the public until the GE animal is approved.<sup>68</sup> The CU Comments argue that “in general, safety and health data should not be considered confidential business information.”<sup>69</sup> They note that although FDA intends to hold public VMAC meetings for the first few GE animals, FDA could easily decide not to hold these meetings after the first few approvals.<sup>70</sup> The third concern is the risk of an incomplete environmental review – that FDA is not the best qualified agency to conduct a comprehensive environmental safety assessment for the animal, and that such assessments should be done instead by the EPA.<sup>71</sup>

Fourth, the CU comments argue that GE foods should be required to be labeled as such, because their difference from non-GE foods is a “material difference”, and is against strong consumer interest. First, CU argues that FDA’s guidance is inconsistent with the FDCA by rendering the labeling of the food “misleading”, by failing to disclose the rDNA construct as an “ingredient” in the food.<sup>72</sup> Second, it argues that strong consumer interest renders the difference

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<sup>66</sup> Consumers Union, Comments on Docket No. FDA-2008-D-0394, “Draft Guidance for Industry: Regulation of Genetically Engineered Animals Containing Heritable rDNA Constructs” (Nov. 18 2008), *available at* <http://www.consumersunion.org/pub/pdf/FDA-comm-DNA-1108.pdf> [hereinafter CU Comments].

<sup>67</sup> *Id.* at 1.

<sup>68</sup> *Id.* at 2.

<sup>69</sup> *Id.*

<sup>70</sup> *Id.*

<sup>71</sup> *Id.* at 3.

<sup>72</sup> *Id.* at 6. The comments cite *United States v. Anderson Seafoods, Inc.*, 447 F. Supp. 1151 (N.D. Fla. 1978) for the proposition that for “ingredients,” the law distinguishes between substances that are present in the food due to “acts of man” and those present due to “acts of nature;” the former are considered added and therefore subject to labeling while the latter are not. It follows that since rDNA constructs are added by man, they are subject to labeling.

between GE food and non-GE food “material.”<sup>73</sup> It cites a 2008 survey that 95% of consumers agreed that “food products made from genetically engineered animals should be labeled as such.”<sup>74</sup> It also cites an FDA final rule on irradiated food, which required labeling even after a determination that the foods were safe, because widespread consumer interest was a factor indicative of the materiality of irradiation.<sup>75</sup> Similarly, it notes that FDA has required labeling for protein hydrolysates because of materiality based solely on religious concerns of consumers.<sup>76</sup> It also argues that labeling should be required in order to enable tracking of adverse health effects of consumption of GE animals.<sup>77</sup>

Finally, the CU Comments criticize the scientific rigor FDA would apply in its NADA evaluations. For example, they note that while FDA guidance requires molecular characterization “of the article”, the molecular characterization should be much more thorough, including “total number of inserts of transgenic DNA . . . exact chromosomal position of each insert . . . complete (nucleotide) base sequence of each insert; nucleotide base sequence of at least 10kbp of flanking host genome DNA on either side of the insert, including changes in methylation patterns.”<sup>78</sup> In other words, the exact DNA sequences on either end of where the rDNA construct is inserted should be required to be identified so that scientists can better predict how the rDNA will interact with (or potentially interrupt) the genes around it.<sup>79</sup> It also recommended that FDA require stricter assurances of the rDNA’s stability,<sup>80</sup> citing studies demonstrating that rDNA genes in various GE crops were much less stable than previously thought, resulting in

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<sup>73</sup> CU Comments, *supra* note 66, at 6.

<sup>74</sup> *Id.* at 3; see CONSUMER REPORTS NAT’L RES. CTR., FOOD-LABELING POLL 2008 (Nov. 11 2008), *available at* <http://www.greenerchoices.org/pdf/foodpoll2008.pdf>.

<sup>75</sup> CU Comments, *supra* note 66, at 6; 51 Fed. Reg. 13,376 at 13,380 (Apr. 18, 1986).

<sup>76</sup> CU Comments, *supra* note 66, at 6; 56 Fed. Reg. 28,592 (1991).

<sup>77</sup> CU Comments, *supra* note 66, at 7.

<sup>78</sup> *Id.* at 8.

<sup>79</sup> *Id.* at 8-9.

<sup>80</sup> *Id.* at 11.

abnormalities such as rearranged inserts, partial copies of genes inserted, multiple copies of transgenes inserted, and scrambling of DNA near the border of the transgenic inserts.<sup>81</sup> The CU also highlighted various other ways in which a NADA should involve a more thorough scientific investigation.<sup>82</sup>

Although many of these challenges mimicked those that were brought against the 1992 Policy for plants in *Bio-Integrity Alliance* (and that failed), they are important to note because they highlight potentially troublesome features of the 2009 Guidance (both as a matter of law and as a matter of policy), against which FDA's consideration of recent GE animals can be evaluated. Thus far, there have been three examples of GE animals on which FDA has already made significant decisions: a GE animal used as a pet (the GloFish), a GE animal used as a drug (the ATryn goat), and a GE animal used as food (the AquAdvantage salmon).

### **III. THE GE ANIMAL FRAMEWORK APPLIED: THREE CASE STUDIES**

#### **A. GE Animal as Pet: the GloFish**

Yorktown Technologies genetically engineered a zebra fish to glow in the dark by using an rDNA construct from a sea coral, which it wished to market as an ornamental or pet fish. In 2003, Yorktown sought FDA's views regarding the fish, trademark named the GloFish™.<sup>83</sup> After reviewing the materials submitted by Yorktown and consulting with the Animal and Plant Health Inspection Service (APHIS) of the Department of Agriculture (USDA), FDA issued the following statement:

Because tropical aquarium fish are not used for food purposes, they pose no threat to the food supply. There is no evidence that these genetically engineered zebra danio fish pose any more threat to the environment than their unmodified counterparts which have long

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<sup>81</sup> *Id.* at 9.

<sup>82</sup> *Id.* at 12-14.

<sup>83</sup> Int'l Ctr. For Tech. Assessment v. Thompson, 421 F. Supp. 2d 1, 4 (2006).

been widely sold in the United States. In the absence of a clear risk to the public health, FDA finds no reason to regulate these particular fish.<sup>84</sup>

The fish was made commercially available immediately thereafter.<sup>85</sup> No other agency, including the EPA and USDA, attempted to regulate the GloFish.<sup>86</sup>

This (in)action was challenged in federal district court in *Int'l Ctr. For Tech. Assessment v. Thompson*, when plaintiffs alleged that FDA's decision not to require Yorktown to follow NAD procedures was arbitrary and capricious, and failed to satisfy FDA's NEPA obligations.<sup>87</sup> The court dismissed both arguments, first holding that FDA's decision *not* to regulate the GloFish lay within the agency's enforcement discretion and thus beyond judicial review.<sup>88</sup> Second, it held that FDA did not violate NEPA by failing to prepare an EIS because its decision was not a "major federal action." It reasoned, "NEPA applies only to agency actions 'even if inaction has environmental consequences'."<sup>89</sup> Because the decision not to regulate was merely agency "inaction", NEPA's requirements were not triggered.<sup>90</sup>

At least one commentator has argued that *Thompson* was wrongly decided. The argument first contends that under the FDCA, FDA is *mandated* to review a NADA or else an animal drug "shall be deemed unsafe" and therefore "adulterated", and adulterated drugs are prohibited from delivery or introduction into interstate commerce.<sup>91</sup> Thus, it is illegal for FDA to allow GloFish to be sold without conducting a NAD assessment. Second, it argues that the refusal to regulate

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<sup>84</sup> FDA, Statement Regarding Glofish, XVIII, No. 6 *FDA Veterinarian Newsletter* Nov./Dec. 2003, available at <http://www.fda.gov/AnimalVeterinary/NewsEvents/FDAVeterinarianNewsletter/ucm106233.htm>; see Thompson, 421 F. Supp. 2d at 5.

<sup>85</sup> *Id.* at 5.

<sup>86</sup> Rekha K. Rao, *Mutating Nemo: Assessing the Environmental Risks and Proposing the Regulation of the Transgenic GloFish™*, 57 ADMIN L. REV 903, 906 (2005).

<sup>87</sup> Thompson, 421 F. Supp. 2d at 5. It also argued that the agency's decision was in violation of the Endangered Species Act, a claim the court also dismissed. *Id.*

<sup>88</sup> *Id.* at 6.

<sup>89</sup> *Id.* at 8, quoting *Defenders of Wildlife v. Andrus*, 627 F.2d 1238, 1243 (D.C.Cir.1980).

<sup>90</sup> Thompson, 421 F. Supp. 2d at 9.

<sup>91</sup> 21 U.S.C. §§ 360b(a)(1), 351(a)(5), 3331(a) (2000); see Rebecca M. Bratspies, *Glowing in the Dark: How America's First Transgenic Animal Escaped Regulation*, 6 MINN. J.L. SCI. & TECH. 457, 478 (2005).

the GloFish was in fact a major federal action, citing *Found. on Econ. Funds v. Heckler*, in which the D.C. Circuit enjoined the NIH from approving the release of a GE bacterium into the environment without first conducting an EIS and reasoned “NEPA would be toothless if agencies could merely issue a conclusory statement that the action did not significantly affect the environment (and that therefore no EIS was required)”.<sup>92</sup> Finally, the commentator argued that FDA’s decision was improper as a matter of policy: “With its GloFish decision, FDA ripped a large hole in the regulatory net--a hole through which all transgenic ornamental fish, and quite possibly all pets, may escape.”<sup>93</sup>

A few lessons emerge from the GloFish example. For one, while FDA asserts its authority over all NADs, it seems only concerned about regulating GE animals when they constitute food or drugs – even if the animals are sold to the public in some fashion. It shows that FDA still considers GE animals to be presumptively safe, by failing to conduct any safety assessment into the animal just because it had been genetically engineered. It also demonstrates that in some cases, environmental assessments of GE animals released to the public are not being conducted by *any* agency whatsoever. Finally, *Thompson* suggests that as in *Alliance for Bio-Integrity*, FDA will be largely protected from judicial review of its (in)actions with regards to GE animals, but by a new, additional shield, enforcement discretion.<sup>94</sup>

### **B. GE Animal as Drug: the ATryn Goat**

GTC Biotherapeutics developed a goat genetically engineered to produce the human protein antithrombin in its milk. Antithrombin is an important blood coagulant, of which a small subset of the human population is deficient in due to a hereditary disorder; the biologic produced

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<sup>92</sup> *Foundation on Econ. Trends v. Heckler*, 756 F.2d 143, 146 (D.C. Cir. 1985).

<sup>93</sup> Bratspies, *supra* note 91, at 478-79.

<sup>94</sup> It is also worth noting that *Thompson* contained no challenge for FDA’s decision to use the NAD provisions to regulate GE animals. Although the 2009 guidance had not yet been issued, FDA had previously employed the same statutory interpretation at the time of the GloFish.

by the goat is recombinant human antithrombin III, called ATryn.<sup>95</sup> In February 2009, FDA approved both the NADA for the GE animal through the CVM, as well as the safety and efficacy of the biologic for human use through the Center for Biologics Evaluation and Research (CBER).<sup>96</sup> Although there was no opportunity for the public to comment on the GE animal before it was approved, FDA conducted an EA on the use of the rDNA construct in the goat,<sup>97</sup> which it published along with the NADA after approval.<sup>98</sup>

The EA entails a thorough review into the safety and stability of the rDNA construct over seven generations of goats,<sup>99</sup> as well as into the efforts made to contain the GE goats from escaping. The goats are housed in two facilities in Massachusetts and Pennsylvania, and all are penned by two levels of physical containment, and are identified by ear tattoos, neck tags, and electronic transponders that allow them to be easily tracked if they somehow escape.<sup>100</sup> The EA noted that the lack of known feral goat populations in Pennsylvania or Massachusetts made any breeding before location of the GE goat extremely unlikely.<sup>101</sup> Precautions are also taken to make sure that their bodily products are incapable of entering the food supply.<sup>102</sup> After reviewing GTC's EA, FDA concluded that "the action will not have a significant effect on the quality of the

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<sup>95</sup> FDA, News Release: FDA Approves Orphan Drug ATryn to Treat Rare Clotting Disorder (Feb. 6, 2009), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm109074.htm>.

<sup>96</sup> *Id.*

<sup>97</sup> FDA, ENVIRONMENTAL ASSESSMENT FOR THE BC6 rDNA CONSTRUCT IN GTC 155-92 GOATS EXPRESSING RECOMBINANT HUMAN ANTITHROMBIN III (RHAT OR ATRYN) (Jan. 29 2009), available at <http://www.fda.gov/downloads/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/UCM163814.pdf> [hereinafter ATryn EA].

<sup>98</sup> FDA, FREEDOM OF INFORMATION SUMMARY: ORIGINAL NEW ANIMAL DRUG APPLICATION, NADA 141-294 (Feb. 6 2009), available at <http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/UCM118087.pdf> [hereinafter ATryn NADA].

<sup>99</sup> For example, "CVM reviewed (a) the quality of the sequencing, (b) the number of insertion sites, and (c) the insertion site itself, including possible disruption of other genes and analysis of open reading frames (ORFs) within and around the insertion site." *Id.* at 7. However, it did not publicize what these precise findings were.

<sup>100</sup> ATryn EA, *supra* note 97, at 17, 19-20.

<sup>101</sup> *Id.* at 20.

<sup>102</sup> *Id.*

human environment”, leading to a finding of no significant impact (FONSI).<sup>103</sup> Because FDA reached a FONSI, it was thus not required to prepare an EIS under NEPA.<sup>104</sup>

The ATryn goat example demonstrates that while FDA does not seem to have an interest in regulating GE animals used for pets, in stark contrast it seems to require in practice a thorough regulation of GE animals used for drugs (apart from the evaluation of the drug itself), in line with the 2009 Guidance. It suggests that in complying with NEPA, FDA would prefer to have the producers satisfy FDA of its environmental safety to allow a FONSI, rather than require FDA to submit an EIS. Also, the ATryn case demonstrates that although the 2009 Guidance initially envisioned a public hearing before the approval of each GE animal, such publicity equally could not occur if FDA does not desire it, as it was absent in this case. Similarly, while it evidenced that the CVM was conducting an extremely thorough review into the safety of the rDNA construct to the animal and to humans, it might not publish the findings on which those conclusions depended (e.g. characterization of the insertion site, etc., comparisons of goat phenotypes, etc.).

Finally, the ATryn goat raises an ethical issue of inserting a human gene into an animal, creating in some sense a human-animal hybrid. While the issue did not draw much public criticism, FDA has still stated that such ethical issues are beyond its jurisdiction.<sup>105</sup> However, this type of genetic manipulation might be greatly disconcerting to some, and the lack of public notification prior to approval exacerbates this concern.

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<sup>103</sup> FDA, FINDING OF NO SIGNIFICANT IMPACT FOR THE BC6 rDNA CONSTRUCT IN GTC 155-92 GOATS EXPRESSING RECOMBINANT HUMAN ANTITHROMBIN III (RHAT OR ATRYN) (Feb. 6, 2009), *available at* <http://www.fda.gov/downloads/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/UCM163815.pdf> [hereinafter ATryn FONSI].

<sup>104</sup> *Id.* at 1.

<sup>105</sup> FDA, VMAC Meeting: AquAdvantage Salmon, at 46:1-9 (Sep. 19, 2010), “while there may be valid [ethical] concerns like that . . . they don’t fall within those standards for approval.”, transcript available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/UCM230469.pdf> [hereinafter Sep. 19 AAS Hearing].

### C. GE Animal as Food: the AquAdvantage Salmon

Currently before FDA is the “elephant in the room”: a salmon that would be the first GE animal to be marketed as human food, which is close to approval.<sup>106</sup> Aqua Bounty has genetically engineered Atlantic salmon with a gene from Chinook salmon that allows it to grow twice as fast as its normal Atlantic salmon. The gene makes the fish produce growth hormone year round instead of only seasonally. The resulting AquAdvantage® salmon (AAS) do not ultimately grow any larger than their non-GE counterparts, but just reach adult size faster.

#### 1. Pending NADA Approval

In September 2010, after a public notice, VMAC held public hearings on the NADA approval of the fish as food and whether FDA should require it to be labeled. It has made the NADA itself public, as well as Aqua Bounty’s EA. Although to date FDA has not yet approved the NADA, according to Larisa Rudenko, a senior official at CVM, the fact that there has been a VMAC meeting is a “really good sign that we’re approaching completion.”<sup>107</sup> FDA compiled the data from Aqua Bounty’s NADA, evaluated it, and gave its evaluation and recommendations to VMAC in a 180-page Briefing Packet. The Briefing Packet indicated that the rDNA construct was stable over seven generations,<sup>108</sup> there were no significant differences found between the food produced by AAS and non-GE salmon,<sup>109</sup> and there were not any “biologically significant” health differences between AAS and non-GE salmon.<sup>110</sup> Importantly, the Briefing Packet listed in great detail all of the relevant studies that had been conducted on AAS salmon by Aqua Bounty and others, allowing public access to the same data FDA has in making its determination.

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<sup>106</sup> Bratspies, *supra* note 91, at 493.

<sup>107</sup> Sep. 19 AAS Hearing, *supra* note 105, at 18.

<sup>108</sup> FDA CVM, BRIEFING PACKET: VMAC, AQUADVANTAGE SALMON 24 (Sep. 20, 2010), *available at* <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/UCM224762.pdf> [hereinafter AAS Briefing Packet].

<sup>109</sup> *Id.* at 24.

<sup>110</sup> *Id.* at 107.



As for environmental impact, FDA indicated that it expected to issue a FONSI because Aqua Bounty was found to have taken adequate measures to prevent the escape of AAS or its genes into the wild.<sup>111</sup> Under the current plan, AAS eggs will be produced in Prince Edward Island, Canada. The eggs will then be shipped to a facility in the highlands of Panama, where they will be grown and processed, and then the processed fish will be returned to the United States.<sup>112</sup> Both facilities are land-based, and involve multiple physical forms of containment, such as screens, nets, and fences. Additionally, it is believed that the conditions of the water around the facility in Panama are generally extremely unfavorable for any escaped AAS salmon to survive.<sup>113</sup> Furthermore, the fish are designed so that if they were to escape, reproduction would be extremely unlikely: all AAS are designed to be females and triploid, meaning they have three sets of chromosomes and are thus rendered sterile.<sup>114</sup> FDA concluded that these “multiple and redundant” barriers to AAS escaping or reproducing led to the inclination of FONSI.<sup>115</sup>

Finally, because of the uncertainty of some of the science and the desire to ensure the rDNA construct remains stable and safe, the report detailed a plan for post-approval safety surveillance of the fish and facilities.<sup>116</sup> Such surveillance will include monitoring of randomly selected AAS fish for morphologic irregularities, rDNA construct stability, and triploidy.<sup>117</sup> The report concluded that such measures were acceptable to address FDA’s minor concerns about the phenotypic characterization of the fish.<sup>118</sup>

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<sup>111</sup> *Id.* at 111-12. The AAS Briefing Packet also states that this determination was based on Aqua Bounty’s EA document and “additional available information . . . including inspection and site visit records.” *Id.* at 111.

<sup>112</sup> *Id.* at 110.

<sup>113</sup> *Id.* at 123-24.

<sup>114</sup> *Id.* at 125-26. It admits that the induction of sterility is not 100% successful. *Id.*

<sup>115</sup> *Id.* at 130, 141-42.

<sup>116</sup> *Id.* at 68.

<sup>117</sup> *Id.* at 58, 68.

<sup>118</sup> *Id.* at 68.

## 2. Labeling

Immediately after the public hearing on the safety of AAS salmon, FDA held a public hearing just to address the issue of labeling, hosted by the Center for Food Safety and Applied Nutrition (CFSAN).<sup>119</sup> Prior to the hearing, FDA issued to the public a “Background Document” on the principles of labeling, reiterating the position of the 2009 Guidance that the differences between AAS and non-GE salmon would only be “material” if they “differ materially in nutritional value, organoleptic properties, or functional characteristics”.<sup>120</sup> Moreover, because the AAS Briefing Packet stated the conclusion that “there are no material differences in food from ABT [AAS] salmon and other Atlantic salmon”,<sup>121</sup> it seems almost certain that FDA’s ultimate determination will be not to require labeling of AAS salmon regardless of the hearing.

## 2. Comments and Criticism

Given the opportunity for public comment and criticism of the AAS fish, Consumers Union submitted another scathing comment. First, it complained that the public was only given 14 days to review the materials before the public hearing, which was not enough to conduct a thorough review of all the information, and asked that the period be extended to 60-90 days.<sup>122</sup> That request was not granted. Second, it contested that the VMAC was not comprised of sufficiently experienced experts, because it “lacks any scientists whose primary expertise is in food allergies, endocrinology or fish ecology, the main topics on which the VMAC will have to render judgments in order to conclude that the salmon is safe.”<sup>123</sup>

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<sup>119</sup> FDA, BACKGROUND DOCUMENT: PUBLIC HEARING ON THE LABELING OF FOOD MADE FROM THE AQUADVANTAGE SALMON 2 (Aug. 2010), *available at* <http://www.fda.gov/downloads/Food/LabelingNutrition/FoodLabelingGuidanceRegulatoryInformation/Topic-SpecificLabelingInformation/UCM223913.pdf>.

<sup>120</sup> *Id.* at 5.

<sup>121</sup> AAS Briefing Packet, *supra* note 108, at 109.

<sup>122</sup> Letter from Jean Halloran, Food Policy Initiatives Director, to Margaret Hamburg, FDA Commissioner (Sep. 15 2010), *available at* <http://www.consumersunion.org/pdf/FDA-ltr-GE-salmon.pdf>.

<sup>123</sup> *Id.*

Its next criticisms charged that the data comprised in the NADA were insufficient to allow FDA to reach a conclusion of the safety of AAS to humans, animals, and the environment, and was scientifically unsound.<sup>124</sup> It noted that the sample size of the allergenicity study was too small at only six fish; that Aqua Bounty manipulated the IGF-1 (a potentially dangerous hormone) data by dropping unfavorable data points; that it was improper for FDA to conclude that there were “insignificant differences” between growth hormone levels in the flesh of AAS and non-GE fish, because in reality it had no data at all on those hormone levels due to insensitive test methodology; and that none of the phenotypic data were scientifically reliable because the tests were conducted on fish raised at the Prince Edward Island Facility and not in Panama where all the marketed fish will be raised, and FDA itself even admitted there are significant differences in the conditions at the two facilities that would affect the phenotype of the fish.<sup>125</sup>

These comments appear to launch a serious assault on the legitimacy of the underlying science that led FDA to its preliminary conclusions. Its characterization of the VMAC as not sufficiently experienced is also disconcerting. Perhaps the fact that FDA has delayed significantly since its September hearing to approve AAS salmon demonstrates a lack of confidence in those initial findings presented to VMAC.

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<sup>124</sup> Consumers Union, Comments on Docket No. FDA-2008-D-0394, “Draft Guidance for Industry: Regulation of genetically engineered animals containing heritable rDNA constructs” (Nov. 18 2010), *available at* <http://www.consumersunion.org/pub/pdf/FDA-comm-DNA-1108.pdf> [hereinafter CU AAS Comments]. Similar concerns to the ones enumerated here were voiced in the public hearing itself. FDA, VMAC Meeting: AquaAdvantage Salmon (Sep. 20 2010), *available at* <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/UCM230471.pdf>.

<sup>125</sup> CU AAS Comments, *supra* note 123, at 1-2. “FDA appears willing to conclude that there are no animal or human safety problems from AquaAdvantage salmon raised in Panama based on *no data at all* from fish raised in Panama even as they admit that the effect of the different culture and 3 rearing conditions on the phenotype of the GE salmon is unknown.” *Id.* at 2-3.

Congress has also taken efforts to block both FDA's approval of AAS and its putative intent not to label. In January 2011, bills were introduced in both the House and Senate, one to prohibit the approval of food from all GE fish entirely and the other to require the labeling of the GE fish.<sup>126</sup> Currently, both bills are at the committee stage.

## **IV. CONCLUSIONS AND RECOMMENDATIONS**

### **A. Conclusions**

The three case studies provide prime examples for evaluating FDA's 2009 Guidance. In short, the cases demonstrate that the policy of the 2009 Guidance, to use the new animal drug framework to govern GE animals and their products, is awkward and problematic. For one, FDA's interpretation has resulted in an overbroad assertion of authority by FDA over animals it clearly has no intent of regulating. According to FDA's Mission, it must "protect the public health by ensuring that -- foods are safe, wholesome, sanitary, and properly labeled; human and veterinary drugs are safe and effective; there is reasonable assurance of the safety and effectiveness of devices intended for human use; cosmetics are safe and properly labeled; and public health and safety are protected from electronic product radiation".<sup>127</sup> Given this mission, it is not surprising or troubling that FDA has chosen not to regulate all GE lab animals, given the lack of implication of the public welfare and enormous variety of experiments at research institutions, which are already checked by other internal mechanisms such as Institutional Review Boards. Nor is it troubling in itself that FDA is not regulating GE animals used as pets – again, they are seemingly beyond its purview.

#### 1. The current policy does not adequately consider environmental risks of GE animals.

What is troubling about the GloFish example, however, is that it demonstrates how the

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<sup>126</sup> S. 229, S. 230, H.R. 251, 112th Cong. Sess. (2011).

<sup>127</sup> 21 U.S.C.A. § 393(b)(2) (2011).

2009 Guidance, combined with the inaction of other agencies, gives short shrift to environmental risks of GE animals. Per the GloFish, *nobody* is regulating GE pets (except the industry itself), leaving their potential for environmental damage untested. The EPA is probably the best agency for this, however, and at least one commentator has argued that the EPA has statutory authority to regulate GE pets under the Toxic Substances Control Act (TSCA).<sup>128</sup> Moreover, it is not clear why FDA should need to conduct *no* environmental assessment for a transgenic fish people do not eat, yet need to conduct a painfully exacting environmental assessment for a transgenic fish people do eat, including multiple redundant genetic and physical barriers to escape. This is just one of the consequences of FDA “trying to force a square peg into a round hole” in its 2009 Guidance.<sup>129</sup>

Perhaps this problem demonstrates the inadequacy of the NEPA system to cope with GE organisms. The system requiring agencies to conduct their own EAs is more appropriate when an agency action is more akin to the release of a single chemical or toxin; GE is unique and different because the “substance” that could be released in the environment is itself capable of reproducing and altering an entire ecosystem through evolutionary biology (recall the “Trojan gene” example)<sup>130</sup>—an event that would have major environmental implications.<sup>131</sup> Agencies other than the EPA may lack the complex ecological knowledge needed to evaluate the potentially enormous ramifications of a single escape of a GE animal. To bolster this concern, thus far FDA has expressed a strong preference for FONSI over EISs, demonstrating that FDA may wish to keep environmental assessments out of the hands of EPA.

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<sup>128</sup> Rao, *supra* note 86, at 922.; 15 U.S.C. §§ 2601-2691 (2000).

<sup>129</sup> Henry I. Miller, *FDA on transgenic animals—a dog’s breakfast?* 26.2 NATURE BIOTECH. 159 (Feb. 2008).

<sup>130</sup> See text accompanying *supra* note 16.

<sup>131</sup> See Mary Jane Angelo, *Regulating Evolution for Sale: An Evolutionary Biology Model for Regulating the Unnatural Selection of Genetically Modified Organisms*, 42 WAKE FOREST L. REV. 93 (2007).

2. The current policy gives FDA too much discretion in determining which GE articles it will and will not regulate, leaving some articles potentially unregulated.

As a preliminary matter, that FDA has asserted its discretionary authority over broad categories of animals it apparently has no interest in regulating itself should be undesirable under principles of good governance. Second, the failure of the *Thompson* challenge to FDA's refusal to regulate the GloFish demonstrates that the elaborate mechanisms of the 2009 Guidance are purely optional on the part of FDA. Moreover, at least in *Thompson* this discretion did not appear to be limited in any way. That is, while it is not disconcerting that FDA does not have to regulate a pet if it does not want to in its "enforcement discretion," it is disconcerting that FDA by the same reasoning does not have to regulate a *food or drug* produced by a GE animal if it does not wish to, and similarly could avoid any assessment of the animal's environmental impact. This discretion itself may not be problematic if one trusts FDA to accurately weigh the risks against the benefits of GE animals. However, in the current situation, where FDA's 25 year-old policy of substantial equivalence appears out of touch with the modern scientific knowledge of GE organisms, one has far less faith in the agency's discretion.

3. The current policy allows FDA to conduct inadequate inquiries into the safety of GE animals; this is exacerbated by lack of public participation.

Similarly, that the guidance envisions public hearings for the first few GE animals it approves is commendable; yet it is worrisome that this was not done for the *very first* FDA-approved GE animal, the ATryn goat. Moreover, the gravity of the criticisms in the comments to the AquAdvantage fish, demonstrating fundamentally flawed scientific assumptions on which a conclusion of safety to humans and the animal was drawn, highlight the importance of public

input in this process. Once more, the non-mandatory nature of the 2009 Guidance, while allowing FDA maximum flexibility, does not ensure much confidence in the public.

Having GE animals regulated as animal drugs also produces a mismatch in the way the safety evidence before FDA is evaluated, with the Center for *Veterinary Medicine* conducting the primary inquiry into issues such as the safety of a food for human consumption. Although one could argue that FDA is competent enough to correct for this mismatch by placing proper experts on the VMAC, there are at least concerns that in the AquAdvantage case, FDA did no such thing.

Finally, the current scheme leaves out any inquiry into the ethical issues raised by GE animals. Under the current regulatory scheme, if FDA is not looking into such concerns, no one is, and because FDA has stated the concerns are beyond its jurisdiction, literally no one at all is.

## **B. Remedies and Recommendations**

The dysfunction of the entire regulatory approach to GE organisms – assuming that GE organisms are substantially equivalent to non-GE organisms, and as such can be regulated just as well through existing regulatory and statutory structures – has become apparent through the recent plant and animal literature and cases. The assumption of the 1986 Comprehensive Plan, that the product should be regulated instead of the process, is simply outdated and unworkable.

### 1. Congress should act to institute a comprehensive statutory scheme to govern GE animals.

What is most needed is for Congress to overhaul the system and institute a comprehensive scheme for the regulation of GE organisms (although this paper only focuses on GE animals). FDA should remain in its area of expertise and evaluate the safety to humans of all food and drugs produced by GE animals, which would involve a thorough investigation into differences between the living GE animals and their non-GE counterparts (safety to the animal), as well as into the differences between their meat if consumed (safety to humans). FDA should

be mandated to conduct a more exacting inquiry into food safety with a premarket approval system more akin to the standard for non-GRAS food additives than for ordinary unadulterated foods. The EPA should remain in its area of expertise and conduct environmental assessments for all GE animals that are expected to be accessed by the public in any way, whether alive or through food or drugs, regardless of their ultimate human use. As it currently does, the USDA should continue to oversee the slaughtering and shipping of the animal meat. Congress should give explicit authorization to FDA to regulate such GE animals so that it would not have to use the awkward NAD framework, and to the EPA so that its jurisdiction would be clear.

Moreover, Congress must institute a mechanism to consider ethical issues raised by GE animals that FDA has asserted are beyond its jurisdiction – the ethical limits as to what kind of and how many human genes may be inserted into a GE animal, as to what kind of deviations from an animal’s “normal” anatomy and behavior induced by genetic engineering are acceptable, etc. In the same vein, Congress should mandate the labeling of all food derived from GE animals as such, recognizing that such a difference is “material” in any real sense of the word, given the overwhelming consumer interest for personal autonomy and religious reasons, and inherent uncertainty of science of its safety at this point.

2. Litigation challenging the legality of FDA approvals of non-enforcement of GE animals is unlikely to succeed, but could have value.

Although challenges could be raised to FDA’s 2009 Guidance and individual decisions, as in *Alliance for Bio-Integrity* and *Thompson*, they are likely to fail. However, it is possible that a court could see things differently five years after *Thompson*, now that the agency has issued its final guidance, and find that an agency action (or inaction) did rise to the level of being arbitrary and capricious. For example, if FDA were to fail to regulate a much more threatening pet than



the GloFish, and such a challenge were brought, a court might find the inaction to constitute “major agency action” under the meaning of NEPA. Although the commentator who argued that *Thompson* was decided wrongly, citing *Heckler*, took this position, she did not acknowledge that *Heckler* was distinguishable. In that case there was an actual NIH *action* that was enjoined, approval of the release of the bacterium, rather than inaction, as the court found in *Thompson*. However, one could argue that the line between agency action and inaction is purely semantic; i.e., whether there is any relevant difference between FDA *approving* a NAD for a new GE pet (or any other GE animal for that matter), and merely standing by as the unapproved GE pet went on the market unpunished and unregulated. Once more, given the nature of GE animals, which are capable of reproducing by themselves once released, the environmental consequence of a release could be truly major. Thus, perhaps courts would be willing to take a tougher stance than before to make sure that FDA complies with NEPA in its regulation of GE animals.

Additionally, perhaps serious concerns to the scientific rigor of FDA’s determination of safety in a NAD (from manipulation of data, etc.) could in fact rise to the level of finding a NAD approval arbitrary and capricious as well.

3. Internal regulatory change is also unlikely to occur, but is the simplest mechanism for rapid change.

Finally, one could hope that FDA will reevaluate its 2009 Guidance. For example, it could promulgate binding regulations interpreting its statutory authority as limited to GE animals used for food and drugs (still using NAD provisions to assert jurisdiction) and then merely mandate a stricter scheme more in touch with the ultimate use of the animal. This seems to be a plausible interpretation of the NAD statute. It could mandate NADs, EAs, and public hearings (with a sufficient period for the public to review the underlying data) for all GE animals intended

to be used as food or drugs, and change its course on labeling. Allowing the entire process to go through notice and comment would also ensure vigorous public debate over these issues, which has sadly been lacking up to this point. The fact that FDA is conducting public hearings to debate the labeling of AquAdvantage salmon, where such labeling would clearly seem not to be required under the 2009 Guidance, suggests that FDA's opinions may indeed be flexible. All GE animals that are not used for food or drugs, yet expected to be released or sold publicly such as pets, could potentially be evaluated by the EPA asserting its jurisdiction under TSCA.<sup>132</sup>

In sum, for law to work effectively and well, it must be in touch with science. The scientific evidence that GE animals designed through rDNA techniques carry risks that are fundamentally different from those FDA has previously encountered is extremely strong. In tandem with other regulatory agencies, FDA must try its best to keep up with the science, and ensure that the enthusiasm over the enormous benefits of GE organisms is tempered by a thorough examination into the potential dangers of each individual one. Because of the potential magnitude of harm, such thorough examinations should be codified rather than left to the agency to hide behind the shields of *Chevron* deference, non-binding statements of policy, and enforcement discretion such that its decisions are judicially unreviewable. As GE animals continue to make their way into American homes, one hopes that the current holes in the regulatory net are not large enough for too dangerous a fish to swim through – or whatever creature will follow in its wake.

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<sup>132</sup> See generally Rao, *supra* note 86.