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Glowing in the Dark: How America's First Transgenic Animal Escaped Regulation

by

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Articles

Glowing in the Dark: How America's First Transgenic Animal Escaped Regulation

Rebecca M. Bratspies*

If you don't want to scare the public, you'd better have an agency responsible, and you'd better have clear-cut rules, and you'd better mandate that they be followed . . . . We don't have that.[1]

One fish, two fish, red fish, blue fish
Black Fish, blue fish, old fish, new fish.[2]

The first commercially available transgenic[3] (or genetically modified "GM") animal went on sale in the United States on January 5, 2004. The GloFish is an aquarium zebra danio (*Brachydanio rerio)* that was genetically engineered to glow in

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1. Arthur Caplan, Chair of the University of Pennsylvania Center for Medical Ethics, as quoted in Gregory M. Lamb, *GloFish Zoom to Market,* CHRISTIAN SCI. MONITOR, Jan. 22, 2004, at 15.

2. DR. SEUSS, ONE FISH TWO FISH RED FISH BLUE FISH 3-4 (1960).

3. The term "transgenic" refers to an individual with an introduced or novel genetic sequence integrated into its genetic makeup. *See* FOOD AND AGRIC. ORG. OF THE UNITED NATIONS (FAO), FAO GLOSSARY OF BIOTECHNOLOGY FOR FOOD AND AGRICULTURE, *at* http://www.fao.org/biotech/find-formalpha-n.asp (last visited Mar. 18, 2005). Typically this term refers to an organism that has genes from another organism inserted into its genome. That said, some scientists are conducting research into autotransgenic organisms—with addition copies of their own species' genes inserted. For a discussion of research involving autotransgenic organisms, see T.J. Pandian, *Guidelines for Research and Utilization of Genetically Modified Fish,* 81 CURRENT SCI. 1172 (2001), *available at* http://www.ias.ac.in/currsci (last visited Apr. 10, 2005).

the dark.[4] This novelty fish is marketed in every state of the United States except California, where it is banned.[5]

Given the significant public and scientific concerns about the safety and wisdom of this technology, one might have expected the first introduction of a transgenic animal to have been an event marked by the full pageantry of formal regulatory scrutiny. For example, since the federal government has repeatedly announced that transgenic animals will be regulated as "new animal drugs" (NAD), one might have expected an especially rigorous approval process for the first such NAD introduced into interstate commerce. Certainly one might have expected a thorough environmental risk analysis. While these expectations might have been reasonable, in this case the expectations would have been entirely wrong.

Rather than engaging in heightened or even ordinary regulatory scrutiny, the Food and Drug Administration (FDA),

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4. These fish are marketed for aquarium uses under the name Night Pearl Glo fish or TK-1 by Taikong Corporation of Taiwan. *See* TAIKONG CORPORATION, SELECT VERSION, *at* http://www.azoo.com.tw/select.html (last visited Apr. 21, 2005). For a skeptical discussion of these fish, see Andrew Pollack, *So the Fish Glow, But Will They Sell?*, N.Y. TIMES, Jan. 25, 2004, at 5. In 2002, Taiwan became the first country to authorize sales of a genetically modified organism as a pet. According to some reports, 100,000 of the glowing fish were sold in less than a month at $18.60 each. *See* Fact Index, *GloFish, in* WIKIPEDIA, THE FREE ENCYCOLPOEDIA, *at* http://www.fact-index.com/g/gl/glofish.html (last visited February 24, 2005).

5. California law prohibits the import or sale of transgenic fish without a permit or an exemption. *See* CAL. CODE REGS. tit. 14, § 671 (2004). Yorktown Technologies requested an exemption which the California Fish and Game Commission denied on December 3, 2003. *See California Blocks Sales of 'Glofish' Pets*, CNN.COM, Dec. 4, 2003, *at* http://www.cnn.com/2003/TECH/science/12/04/fluorescent.fish.ap/ (last visited February 24, 2005). In March of 2004, the Commission voted 3-1 to seek an updated recommendation from the California Department of Fish and Game on whether GloFish should be granted such an extension, and to hold public hearings before making a final decision. *See* Dan Thompson, *California Reconsiders Nation's Only Bio-Pet Ban*, USA TODAY, Apr. 2, 2004, *available at* http://www.usatoday.com/tech/news/techpolicy/2004-04-02-fishwife_x.htm (last visited Mar. 18, 2005). To aid in its reconsideration, the Commission requested more detailed information from the Department. During the Commission's October 21, 2004 meeting, Agenda Item 10 was an "Update on GloFish Regulatory Timeline" given by the Department of Fish and Game. The Department reported that for an exemption, Yorktown would need to complete an environmental impact report as required by the California Environmental Quality Act. Cal. Fish and Game Comm'n, Meeting Agenda, Oct. 21-22, 2004, *at* http://www.fgc.ca.gov/2004/102104agd.html. Included was testimony by Alan Blake of Yorktown Technologies. *Id.* Audio from that segment of the Commission meeting see http://www.fgc.ca.gov/2004/2004mtgs.html (last visited Mar. 18, 2005).

the lead agency for regulating transgenic animals, instead announced in 2003 that it would permit GloFish to enter into interstate commerce wholly unregulated.[6] This decision not to regulate rested on a three sentence official statement in which the FDA announced that:

> [b]ecause 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 been widely sold in the United States. In the absence of a clear risk to the public health, the FDA finds no reason to regulate these particular fish.[7]

This announcement that the FDA would not to regulate GloFish meant that no federal agency was exercising any oversight over the first commercially-available transgenic animal.

The usual pattern for a new technological innovation is intense regulatory scrutiny of the first market entrant, with follow-on products receiving either comparable treatment or relaxed scrutiny as the agency gains familiarity with the field.[8] Agencies tend to learn during the course of the first application, with later entrants being the beneficiaries of the learning curve.[9] Instead, GloFish offers a textbook example of technological progress outpacing policy formation. The regulatory vacuum GloFish revealed has sparked at least one

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6. FDA Statement Regarding Glofish, U.S. Food & Drug. Admin. (Dec. 9. 2003), *available at* www.fda.gov/bbs/topics/NEWS/2003/NEW00994.html (last visited Feb. 24, 2005) [hereinafter Glofish Statement].

7. *Id.*

8. In the 1970s, scientists responded to growing concerns that biotechnology was developing more rapidly than was the ability to understand or manage the risks it posed by developing the Asilomar self-regulation plan. This plan was based on the conviction that standards of care "should be greater at the beginning and modified as improvements in the methodology occur and assessment of the risks change." Paul Berg et al., *Asilomar Conference on Recombinant DNA Molecules*, 188 SCI. 991, 991-92 (1975). This same "go slow and learn from experience" model was certainly expressed in the rhetoric of the Coordinated Framework on Biotechnology. *See* Coordinated Framework for the Regulation of Biotechnology, 51 Fed. Reg. 23,302, 23,305 (June 26, 1986) [hereinafter Coordinated Framework]. These principles continue to resonate powerfully in the context of transgenic fish.

9. For example, the USDA began simplifying its procedures for the introduction of certain genetically engineered plants after gaining experience with the crops. *See* Genetically Engineered Organisms and Products: Simplification of Requirements and Procedures for Genetically Engineered Organisms, 62 Fed. Reg. 23,945 (May 2, 1997). For the simplified procedures see 7 C.F.R. § 340.0 (2004).

lawsuit[10] and has drawn condemnation from scientists and from the pet industry.[11]

GloFish marked a momentous change in the status quo. No longer limited to the relatively controlled realm of experimental research, a transgenic animal is now freely sold in interstate commerce. This watershed event is surely the harbinger of things to come—we can expect a future in which transgenic animals are regularly sold in commerce in the United States and around the world. Proponents of other novel transgenic organisms are already claiming that the GloFish's regulatory path sets a precedent for regulating transgenic organisms.[12] Quite frankly, it was precisely that possibility that prompted this article. A future peopled (so to speak) with transgenic animals may be inevitable, but there is still time to choose the conditions and circumstances under which it will unfold.

Getting regulatory policy right is critical. Only appropriate and consistent regulatory structures will ensure that this new technology is explored in a fashion that protects human health and the environment, while still encouraging innovation. Since the FDA is currently considering a proposal to approve widespread aquaculture of transgenic salmon, the FDA's approach to GloFish raises immediate and pressing concerns

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10. *See* International Ctr. for Tech. Assessment v. Thompson, No. 1:04CV00063 (D.D.C. 2004). Docket entries are available at http://pacer.psc.uscourts.gov (last visited Feb. 24, 2005).

11. For example, PetSmart refused to carry GloFish, citing concerns about the long-term effects of genetic engineering on the fish themselves. *See* Charles Q. Choi & Steve Nash, *GloFish Draw Suit*, THE SCIENTIST, Jan. 7, 2004, *available at* http://www.biomedcentral.com/news/20040107/01/ (last visited Mar. 18, 2005). Similarly, the Ornamental Aquatic Trade Association labeled GloFish "an unwelcome addition to the marketplace," and announced that transgenic fish have no place in the ornamental fish industry. *See* Ornamental Aquatic Trade Association (OATA), *Genetically Modified Ornamental Fish*, *at* http://www.ornamentalfish.org/aquanautstatement/gmfish.php (last updated Aug. 27, 2004). Over eighty percent of the readers surveyed at Practical FishKeeping opposed GM ornamental fish. *See California to Reconsider GM Fish Ban*, PRACTICAL FISHKEEPING, April 2, 2004, *available at* http://www.practicalfishkeeping.co.uk/pfk/pages/item.php?news=247 (last visited Mar. 18, 2005).

12. Simon Brodie, CEO of Allerca, Inc., contends that "[a]s long as people don't start eating cats and they don't enter the food chain, then we should be handled like the GloFish." Paul Elias, *Invention Is Nothing To Sneeze at—Non-allergenic Cat in the Works*, CHI. SUN TIMES, Oct. 28, 2004, *available at* http://www.suntimes.com/output/ news/cst-nws-cats28.html (last visited Mar. 18, 2005).

about the environmental risks likely to flow from inadequate regulation of this new technology.[13]

To explore this issue, Part I of this article provides a brief introduction to transgenic animals and the motivations behind this research. Part II describes the New Animal Drug approval process and measures what the FDA actually did in the GloFish case against the statutory requirements for approving a new animal drug under the federal Food Drug and Cosmetics Act (FDCA). Part III compares the FDA's GloFish Declaration with the FDA's responsibilities under the National Environmental Policy Act (NEPA). Part IV makes the case that in its GloFish decision, the FDA inappropriately substituted "substantial equivalence," an administrative policy developed to coordinate agency oversight of biotechnology, for the applicable statutory standards under the FDCA and NEPA. This section highlights some broader administrative and constitutional implications of the FDA's decision. Finally, Part V explores the possible fallout from this decision for the FDA's pending consideration of a NAD application for transgenic salmon. In particular, this section identifies some *sui generis* environmental concerns associated with aquaculture of transgenic salmon and considers what the FDA's GloFish decision may tell us about the FDA's willingness to fully consider these questions.

I. MAKING TRANSGENIC ANIMALS

In just over a decade, genetic engineering (also called "genetic modification," "GM," or "biotechnology") has emerged as a powerful tool for agricultural production. By transferring genetic material from organism to organism, researchers can create wholly new, transgenic organisms. Many transgenic agricultural plants have already been developed for use in the United States and elsewhere. By 2004, the lion's share of the soybeans, and significant percentages of the corn and cotton grown in the United States were transgenic varieties.[14] There

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13. Opponents of biotechnology have raised a series of human health concerns associated with the proposed use of aquacultured transgenic salmon for food. *See, e.g.*, Janye Kay, *'Frankenfish' Spawn Controversy—Debate over Genetically Altered Salmon*, S.F. CHRON., Apr. 29, 2002, at A4. Those concerns are largely outside the scope of this article, which focuses on environmental issues.

14. The United States accounts for most of the genetically modified crops planted in the world and each year a larger percentage of the American

has been a great deal of public controversy surrounding the use of these transgenic or genetically modified plants.[15] Transgenic animals raise even greater public concern.[16]

GloFish may be the first transgenic animal on the market, but there are many more waiting in the wings. Applications of the technology range from the sublime to the frivolous. Researchers are currently experimenting with producing human blood proteins and other pharmaceuticals in transgenic pigs and other animals.[17] Goats have been genetically modified to produce spider silk in their milk.[18] Allerca, a division of Geneticas Life Science, is currently taking orders for transgenic, allergen-free cats.[19] The central regulatory

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harvest is comprised of GM plantings. In 2004, GM soybeans accounted for 85% of the soybean acreage planted in the United States; GM cotton for 76% of the cotton, and GM corn for 45% of the corn. For these and other data pertaining to GM crops, see PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, AUG. 2004 FACTSHEET, GENETICALLY MODIFIED CROPS IN THE UNITED STATES (Aug. 2004), *at* http://pewagbiotech.org/resources/factsheets/display.php3?FactsheetID=2 (last visited Mar. 19, 2005). The underlying data, as well as a wealth of other information on these crops are provided by the Economic Research Service of USDA at http://www.usda.gov/wps/portal/!ut/p/_s.7_0_A/7_0_1OB?navid=DATA_STATISTICS&parentnav=AGRCULTURE&navtype=RT (last visited Mar. 18, 2005).

15. There are many organizations and advocacy groups trying to restrict or prevent widespread adoption of these crops. Among the most prominent are: The Center for Science in the Public Interest (http://www.cspinet.org/), the Union of Concerned Scientists (http://www.ucsusa.org/), Greenpeace (http://www.greenpeace.org/international_en/), and the Center for Food Safety (http://www.centerforfoodsafety.org/home.cfm).

16. *See* PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, NATIONAL SURVEY (Sept. 27, 2004), *at* http://pewagbiotech.org/research/2004update/ (last visited Mar. 19, 2005).

17. *See* David F. Betsch, *Pharmaceutical Production in Transgenic Animals* (Iowa State Univ., N. Cent. Reg'l Extension, Biotechnology Information Series (Bio-10), 2004), *at* http://www.nal.usda.gov/bic/Education_res/iastate.info/bio10.html (last visited Mar. 19, 2005) (providing a list of some of the pharmaceuticals under development). For an introduction to this issue geared towards the nonscientist see David Gillespie, Genetic Sci. Learning Ctr. at the Univ. of Utah, *Pharming for Farmacueticals*, *at* http://gslc.genetics.utah.edu/features/pharming/ (last visited Mar. 18, 2005).

18. *See* Christopher Helman, *Charlotte's Goat*, FORBES, Feb. 19, 2001, at 101; *GM Goat Spins Web Based Future*, BBC NEWS, Aug. 21, 2000, *at* http://news.bbc.co.uk/1/hi/sci/tech/889951.stm (last visited Mar. 19, 2005).

19. Allerca's website can be accessed at http://www.allercafoundation.org (last visited Mar. 19, 2005). A quick perusal of the site reveals a widespread animal cloning and genetic modification agenda. Among the more bizarre projects is one called NIGHTSAVE which would implant jellyfish genes into deer to create transgenic deer with fluorescent hair and skin when illuminated by car headlights. Although this last project seems like the beginnings of an

questions are real and immediate. Product developers and the concerned public need to know that regulators will scrutinize these novel organisms under credible, consistent, and transparent standards designed to ensure human and environmental safety.

A. WHAT DOES "TRANSGENIC" MEAN?

Legal discussions of biotechnology always begin with the requisite definition section. I suspect that most readers stop there—few lawyers have training in the natural sciences and the jumble of words and concepts tend to leave readers longing for some nice straightforward antitrust or rule against perpetuities issues. It is a real challenge to present an accessible introduction to the technology without oversimplifying to the point of absurdity. Fortunately, lawyers are generally accounted to be quick studies. In the spirit of informing without overwhelming, I offer a relatively simple introduction to the process of creating a transgenic fish and try to direct interested readers to more detailed sources of information.

The Cartagena Protocol on Biosafety[20] provides a useful definitional starting point for a discussion of transgenic organisms (though for purposes of the Protocol, the equivalent term "living modified organism" or "LMO" is used). Under the

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internet hoax, Allerca's CEO Simon Brodie, claims that the project is for real and only needs funding. E-mail from Simon Brodie to Rebecca M. Bratspies (Jan. 14, 2005, 19:48:00 EST) (on file with author).

20. The Cartagena Protocol on Biosafety grew out of Article 19 of the Convention on Biological Diversity, which calls upon Parties to provide for the effective participation in biotechnological research activities and the sharing of its benefits and to consider a protocol on biosafety. Cartagena Protocol on Biosafety to the Convention on Biological Diversity, June 5, 1992, art. 19, 31 I.L.M 818, 830 (1992), *available at* http://www.biodiv.org/doc/legal/cbd-en.pdf (last visited Apr. 24, 2005). The Cartagena Protocol on Biosafety was adopted in January 2000. Secretariat of the Convention on Biological Diversity, *Cartagena Protocol on Biosafety: About the Protocol*, *available at* http://www.biodiv.org/biosafety/background2.aspx (last visited Mar. 19, 2005). The Protocol was opened for signature from May 15, 2000 through June 4, 2001 and received 103 signatures. The Protocol entered into force on September 11, 2003, ninety days after receipt of the 50th instrument of ratification. SECRETARIAT OF THE CONVENTION ON BIOLOGICAL DIVERSITY, CARTAGENA PROTOCOL ON BIOSAFETY: FROM NEGOTIATION TO IMPLEMENTATION, *available at* http://www.biodiv.org/doc/publications/bs-brochure-02-en.pdf (last visited Mar. 19, 2005). The full text of the Cartagena Protocol is available at www.biodiv.org/biosafety. The Protocol currently has 117 parties. *Id.*

Protocol, a living modified organism is "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology."[21] "Modern biotechnology" is further defined to mean various laboratory techniques for introducing novel DNA into cells or organelles.[22] These techniques permit researchers to either physically or chemically transfer new genetic material from any organism to any other organism. The principle criterion for being classified as a technique of modern biotechnology is that the technique "overcome natural physiological reproductive or recombinant barriers" that would otherwise prevent the genetic exchange.[23] Or, in plain English, biotechnology allows scientists to recombine genes themselves without regard for the biological constraints of sexual or asexual reproduction that ordinarily limit gene flow between organisms. This transferred genetic material is the "transgene" in the term transgenic animal.

B. HAVEN'T WE BEEN GENETICALLY MODIFYING ORGANISMS FOR MILLENNIA?

Farmers have certainly been genetically manipulating plants and animals since the dawn of agriculture. Over the millennia, farmers developed animal husbandry techniques for selectively breeding livestock to enhance useful or desirable traits, or to suppress undesirable ones. Selective breeding enabled farmers to exploit the variations naturally present within a species to develop new, more desirable strains.[24] Over time, this process of selective breeding can produce a radically altered species. For example, modern cows, pigs, goats and chickens, all produced through centuries of selective breeding, do not much resemble their wild counterparts and indeed are largely unable to survive in the wild. Unlike modern biotechnology, however, selective breeding can enhance or suppress only those traits already present in a population. No amount of selective breeding could transfer a spider gene to a

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21. Secretariat of the Convention on Biological Diversity, Cartagena Protocol on Biosafety, Jan. 29, 2000, at art. 3(g), 39 I.L.M 1027, 1027 (2000), *available at* http://www.biodiv.org/biosafety/articles.asp?lg=0&a=bsp-03 (last visited Mar. 19, 2005).

22. *Id.*

23. *Id.* There is an additional requirement that the technique not be one used in traditional breeding or selection.

24. For an explanation of these points, accessible to the non-scientist see generally *Feeding the Five Billion*, ECONOMIST, Nov. 10, 2001.

goat[25] or a jellyfish gene to a zebrafish.[26]

Modern biotechnology has expanded the process of genetic modification tremendously. Functional genes can be isolated and transferred to an animal from any organism—across species, class, phylum and kingdom. In other words, genetic engineering enables breeders to recombine genes themselves. This technology can create organisms that could not exist without such intervention.

In many ways, the revolution of biotechnology "is pushing society into rethinking what we want out of agriculture."[27] There are new possibilities for human intervention in the biological world that never before existed. Most will agree that this new technology poses both risks and benefits. Unfortunately, in the vigorous public debate, advocates on all sides are tempted to obscure either the benefits or the risks in order to sway public opinion. While it is certainly true that very few organisms that are part of the human environment have escaped human genetic modification, claims that modern biotechnology is somehow "more of the same" are often so simplistic as to border on the absurd. Hyperbolic claims that biotechnology necessarily involves "playing god with nature," are equally reductionist. These intellectual shortcuts do little to further discourse and should be abandoned. The public debate between supporters and opponents of biotechnology will certainly continue for the foreseeable future—there are genuine philosophical differences between the various camps. Moreover, the technology is far too new for us fully to understand its long-term costs and benefits. That said, the extremes of the discussion seem totally out of step with how this transformative technology fits into a history of human re-creation of the natural world.

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25. *See GM Goat Spins Web of the Future*, BBC NEWS, Aug. 21, 2000, *available at* http://news.bbc.co.uk/1/hi/sci/tech/889951.stm (last visited Apr. 22, 2005).

26. This is, of course, the genetic modification that gave rise to the GloFish. For a detailed description of this process, see *infra* section I.C.

27. BRIAN JOHNSON, CONSULTIVE GROUP ON INT'L AGRIC. RESEARCH, GENETICALLY MODIFIED CROPS AND OTHER ORGANISMS: IMPLICATIONS FOR AGRICULTURAL SUSTAINABILITY AND BIODIVERSITY 131, *at* http://www.cgiar.org/biotech/rep0100/Johnson.pdf (last visited Mar. 19, 2005).

C. WHY MAKE A TRANSGENIC FISH?

Assuming that one intends to make a transgenic animal, there are many reasons to begin with fish. It is an unfortunate fact that the success rates for creating transgenic animals are quite low—about ten percent.[28] Out of every one hundred organisms subject to the biotechnology techniques described above, only about ten will be transformed, meaning they will integrate and express the transgene.[29] And, expression of the novel genetic material is only the first step. Researchers are looking for individuals that not only express the transgene themselves but also can pass it on to offspring generated through normal reproduction. Altering the heritable genome is the ultimate goal of these laboratory processes. A much smaller percentage (about one percent) of individuals expressing the transgene meet this test.[30]

Because of these low success rates, two unique aspects of fish biology make fish a particularly attractive candidate for genetic engineering. First, female fish produce eggs in the millions. This sheer fecundity makes it easy for researchers to obtain the large supply of eggs needed for experimentation purposes (egg availability is often a limiting factor in mammalian experimentation and is a concern frequently raised in the context of human stem cell research).[31] Moreover, in the ordinary course, fertilized fish eggs develop outside the fish's body—making *in vitro* cultivation of the newly modified organisms a simpler and cheaper prospect for fish than for

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28. *See* John Beardmore & Joanne Porter, *Genetically Modified Organisms and Aquaculture*, FAO FISHERIES CIRCULAR NO. 989 3-8 (2003) [hereinafter FAO FISHERIES].

29. Techniques for creating transgenic organisms typically include microinjection, electroporation, use of microprojectiles and liposome mediated transformation. Microinjection has been the preferred technique to introduce novel genetic material to fish egg. *See* FAO FISHERIES, *supra* note 28, at 3-8. For a description, complete with diagrams, of the techniques of genetic engineering geared towards the lay reader, see PEW INST. ON FOOD & BIOTECHNOLOGY, FUTURE FISH: ISSUES IN SCIENCE AND REGULATION OF TRANSGENIC FISH 7-9 (2003), *available at* http://pewagbiotech.org/research/fish/fish.pdf (last visited Mar. 19, 2005) [hereinafter FUTURE FISH].

30. *See* FAO FISHERIES, *supra* note 28, at 11.

31. *See* FUTURE FISH, *supra* note 29, at 4-5. In January of 2004, just as GloFish were reaching stores, Japanese and United States researchers announced an innovative technique to genetically modify zebrafish using sperm cells grown in vitro, rather than eggs. *See* Kayoko Kurita et al., *Transgenic Zebrafish Produced by Retroviral Infection of In Vitro Cultured Sperm*, 101 PROCEEDINGS NAT'L ACAD. SCI. 1263, 1263-67 (Feb. 3, 2004).

mammals. Together, the large supply of fish eggs and the relatively easy laboratory development of transformed eggs mean that experimentally transformed fish can be grown in large number. Experimental success is thus more likely.

D. GLOFISH: THE FIRST TRANSGENIC FISH SOLD IN INTERSTATE COMMERCE

GloFish are the first transgenic animal to be sold commercially in the United States.[32] Through genetic engineering, a research group at the National University of Singapore created GloFish by adding a gene for a red fluorescent protein from a sea anemone to conventional zebrafish.[33] Thanks to this gene, the normally black-and-silver zebrafish glow bright red under black or ultraviolet light. The Singapore laboratory that produced GloFish was engaged in research aimed at developing a biological system for pollution detection,[34] but novelty aquarium use has become the commercial driver for production of GloFish.

Texas-based Yorktown Technologies purchased exclusive international marketing rights for GloFish in early 2003. Through contracts with two large Florida purveyors of aquarium fish (5-D Tropical and Segrest Farms),[35] Yorktown produces GloFish for commercial sale throughout the United States.[36] In addition to the red GloFish currently on the market, Yorktown expects to market fluorescent green, orange, and yellow GloFish in the near future.[37] While zebrafish are

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32. Zebra danao, which were modified to create GloFish, are a standard of laboratory research. The genome of the fish has been well characterized, and can model many biological systems useful for research.

33. *See* Zhiyuan Gong et al., *Development of Transgenic Fish for Ornamental and Bioreactor by Strong Expression of Fluorescent Proteins in the Skeletal Muscle*, 308 BIOCHEMICAL & BIOPHYSICAL RES. COMM. 58, 58-63 (2003).

34. *See* Nat'l Univ. of Singapore, Zebra Fish as Pollution Indicators, *at* http://www.nus.edu.sg/corporate/research/gallery/research12.htm (last visited Mar. 19, 2005).

35. In Florida, aquaculture is big business, with farm gate receipts valued at $99 million in 2001. *See* DIV. OF AQUACULTURE, FL. DEP'T OF AGRIC. AND CONSUMER. SERVS., 2003-2004 FLORIDA AQUACULTURE PLAN 3, *available at* http://www.floridaaquaculture.com/pub.atm (last visited Mar. 19, 2005). Tropical ornamental fish and plants are Florida's most valuable aquaculture products and compose over 60% of the states aquaculture sales. *See id.* at 9.

36. Eric Hallerman, *GloFish, The First GM Animal Commercialized: Profits Amid Controversy*, ISB NEWS REPORT, June 2004, *at* http://www.isb.vt.edu/articles/ jun0405.htm (last visited Mar. 19, 2005).

37. *See* Pollack, *supra* note 4, at 5.

quite inexpensive—each aquarium fish generally sells for around thirty-three cents—the fluorescent GloFish are priced between $5 and $15 each.[38] Yorktown declines to make public its sales figures for GloFish,[39] but newspaper reports indicate that in the weeks following their release, the company claimed to have sold tens of thousands of the transgenic fish.[40]

E. THE FOCUS OF RESEARCH

Although this article takes GloFish as its starting point, transgenic ornamental fish are really a side note to the broader discussion of regulating transgenic fish. The vast majority of research effort has been devoted to modifying high value food fish to make them better suited for aquaculture. Currently, the fastest growing sector of aquaculture involves raising carnivorous fish for western markets.[41] Many of aquaculture's most vocal boosters are promoting aquaculture of transgenic fish. It is this prospect of large-scale aquaculture[42] of genetically engineered food fish, especially salmon and similar high-value carnivorous fish, that has the aquaculture industry salivating, and many policymakers scared.

The first reports of the application of genetic engineering to fish appeared in the 1980s.[43] Since then, there has been a

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38. *See* Dawn Fallilk, *GloFish Filling Trendy Tanks*, PHIL. INQUIRER, Jan. 12, 2004, at A1.

39. Personal Communication from Yorktown Technologies (on file with author).

40. Chang Ai-Lien, *GloFish Sparks off Classroom Study in US*, STRAITS TIMES, Feb. 25, 2004.

41. *See* FAO FISHERIES, *supra* note 28, at 18.

42. Dwindling wild stocks and high market prices have made salmon a particularly attractive candidate for aquaculture. K. Sandnes & A. Ervick, *Industrial Marine Fish Farming*, *in* SUSTAINABLE AQUACULTURE 97, 97 (N. Svennevig et. al. eds., 1999). By the late 1990s, salmon aquaculture was producing over 900,000 tons of fish per year. *See id.* In the United States alone, sale of carnivorous aquaculture products, largely salmon, has grown from $45 million in 1974 to over $1.1 billion in 2000, and is a $200 million euro business in the European Union. *See* PRICE WATERHOUSE COOPERS, NORTHERN AQUACULTURE STATISTICS 2000—YEAR IN REVIEW, *at* http://ocad-bcda.gc.ca/enetresults2000.pdf (last visited Mar. 19, 2005); CENT. STATISTICS OFFICE IRELAND, FISHERIES STATISTICS 2002 (2003), *at* http://www.cso.ie/releasespublications/documents/agriculture/current/fishery.pdf (last visited Mar. 3, 2005). The United States Department of Commerce has publicly committed itself to building domestic aquaculture into a $5 billion industry by 2025—a five-fold increase from 2001 levels. *See* U.S. DEP'T OF COMMERCE, AQUACULTURE POLICY, *at* http://www.nmfs.noaa.gov/ocs/tradecommercial/DOCAQpolicy.htm (last visited Mar. 19, 2005).

43. *See* N. Maclean & S. Talmar, *Injection of Cloned Genes Into Rainbow*

burst of genetic modification activity in aquaculture research and development. Indeed, by 1990, fourteen species of transgenic food fish had been produced in laboratories around the world,[44] and in 2003, the FAO reported twenty-three aquatic transgenic species.[45] The majority of the research and development efforts to date have focused on improving growth rates or efficiency of food conversion for salmon (and similar food fish) raised through aquaculture.[46] Through insertion of additional copies of fish growth hormone (GH) genes,[47] coupled with mammalian promoters, researchers have been able to accelerate fish growth rates, with modified fish growing two to eleven times faster than their non-modified counterparts.[48] Increased growth means that fish reach marketable size sooner, which reduces overhead costs for fish farmers.[49] Under

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Trout Eggs, 82 J. EMBRYOLOGY & EXPERIMENTAL MORPHOLOGY 187, 187 (1984); Z. Zhu et al., *Novel Gene Transfer into the Fertilized Eggs of the Goldfish (*Carassius acuratus *L. 1758)*, 1 J. APPLIED ICHTHYOLOGY 31, 31-34 (1984).

44. *See* A. R. Kapuscinski & E.M. Hallerman, *Implications of Introduction of Transgenic Fish into Natural Ecosystems*, 48 CAN. J. FISHERIES & AQUATIC SCI. 99, 100 (1991). This figure does not include the use of transgenic fish as a research model within laboratories exploring basic biological questions, but only those modifications intended to alter traits to make fish more economical to grow, more nutritious, or otherwise more desirable to consumers and producers.

45. *See* FAO FISHERIES, *supra* note 28, at 3.

46. *See id.* at 2. Creating transgenic fish with increased cold tolerance is a second area of significant research though to date the research has not been as successful. For a chart of transgenic fish under development, see FUTURE FISH, *supra* note 29, at 6.

47. Different transgenes produce different rates of growth. For example, use of an all-fish GH gene construct to make transgenic Atlantic salmon has produced a twofold increase of the transgenic fish growth rate. *See* S.J. Du et al., *Growth Enhancement in Transgenic Atlantic Salmon by the Use of an "All Fish" Chimeric Growth Hormone Gene Construct*, 10 BIO/TECHNOLOGY 176, 178 (1992). Additionally, the use of ocean pout antifreeze promoter and salmon GH genes might produce up to a five-fold to thirty-fold increase in weight after one year of growth. *See* R.H. Devlin et al., *Production of Germline Transgenic Pacific Salmonids with Dramatically Increased Growth Performance*, 52 CAN. J. FISHERIES & AQUATIC SCI. 1376, 1381 (1995); *See also* R.H. Devlin et al., *Transmission and Phenotypic Effects of an Antifreeze/GH Gene Construct in Coho Salmon (*Oncorhynchus kisutch*)*, 137 AQUACULTURE 161, 167 (1995); R.H. Devlin et al., *Brief Communication: Extraordinary Salmon Growth*, 371 NATURE 209, 209 (1994).

48. *See* M.A. Rahman, & N. Maclean,, *Growth Performance of Transgenic Tilapia Containing an Exogenous Piscine Growth Hormone Gene*, 173 AQUACULTURE 333, 334 (1999).

49. For charts documenting this increased growth rate, and a description of the commercial expectations of transgenic fish, see G. L. Fletcher et al.,

laboratory conditions, this increased growth rate has also been correlated with a significant increased efficiency in feed conversion.[50]

The economic attraction of these modifications is obvious. Unfortunately, the very factors that make transgenic fish an attractive commercial prospect might also pose serious risks, not only to wild relatives but to whole ecosystems once these fish escape into the wild. Unlike domestic farm animals, laboratory or farm raised fish easily become feral and compete with indigenous populations.[51] Because of their novel characteristics, transgenic escapees could pose even greater threats to wild population than do conventional fish. The negative consequences could be devastating.

To date, the light regulatory scheme imposed on aquaculture has been wholly unable to resolve the escape problem, and fish farmers seem to treat escaped fish as a cost of doing business. The magnitude of the escape problem prompted National Research Council (NRC) to call for caution in experimentation and commercialization of transgenic fish.[52] The NRC concluded that the many critical unknowns prevented an informed judgment about whether or how to proceed with

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Transgenic Salmon: Potential and Hurdles, PROCEEDING OECD WORKSHOP ON MOLECULAR FARMING HELD IN LE GRANDE MOTTE, FR.,. Sept. 3-6, 2000, *at* http://www.aquabounty.com/ (last visited Mar. 19, 2005).

50. *See* NAT'L RESEARCH COUNCIL, ANIMAL BIOTECHNOLOGY: SCIENCE-BASED CONCERNS 89 (2002), *available at* http://www.nap.edu/openbook/0309084393.html (last visited Apr. 10, 2005) [hereinafter NAT'L RESEARCH. COUNCIL].

51. There is a growing body of evidence that escaped aquaculture fish are fully capable of establishing themselves in the environments to which they escape. This phenomenon already poses ecological risks to wild salmon stocks. *See* NAT'L RESEARCH COUNCIL, *supra* note 50, at 90-91. Recent studies indicate that thirty to forty percent of the Atlantic salmon caught in the Northern Atlantic Ocean originated from farmed fish. *See* L.P. Hansen et al., *High Numbers of Farmed Atlantic Salmon,* Salmo salar *L, Observed in Oceanic Waters North of the Faroe Islands*, 24 AQUACULTURE & FISHERIES MGMT. 777, 777 (1993). In some parts of Norway, fish from farmed origins are the majority of animals captured. *See* H. Saegrov et al., *Escaped Farmed Atlantic Salmon Replace the Original Salmon Stock in the River Vosso, Western Norway*, 54 ICES J. MARINE SCI., 1166, 1167 (1997). On the east coast of North America, escaped farm salmon outnumber wild fish by as much as ten to one in some rivers. *See* ATLANTIC SALMON FED'N, ATLANTIC SALMON AQUACULTURE: A PRIMER, *at* www.asf.ca/backgrounder/asfaquacbackgrounder.pdf (last visited Mar. 19, 2005).

52. *See* NAT'L RESEARCH COUNCIL, *supra* note 50, at 92.

commercialization of transgenic fish.[53] In light of these high stakes, the relaxed, even inattentive, regulatory scrutiny the FDA applied to GloFish appears wildly inappropriate.

II. THE FEDERAL FOOD DRUG AND COSMETICS ACT IS A POOR FIT FOR REGULATING TRANSGENIC ANIMALS

Under a 1986 executive policy known as the Coordinated Framework for the Regulation of Biotechnology Products (the "Coordinated Framework"),[54] many federal agencies jointly supervise the myriad uses and products of biotechnology in the United States. The Coordinated Framework declared that biotechnology products would be evaluated under the same laws and processes used to review products produced without biotechnology.[55] As a result, regulatory control over these products is allocated among various federal agencies based on each agency's historical role under pre-existing statutes.[56] Three agencies, the USDA, the EPA and the FDA have primary regulatory authority over various aspects of biotechnology. These agencies have cobbled together a regulatory structure in which at least ten different pre-existing statutes regulate portions of this new technology. Unfortunately, many transgenic organisms confound conventional regulatory categories. To respond to the *sui generis* challenges posed by these genetically modified organisms (GMOs), regulators rely on increasingly creative interpretations of these existing laws. Transgenic animals are a case in point.

Under the Coordinated Framework, the FDA claims primary regulatory authority over transgenic animals, including fish, by virtue of its "new animal drug" authority under the FDCA.[57] The FDCA provides a comprehensive scheme to protect the public from drugs that may be unsafe or ineffective for their intended uses. As part of this scheme, the Act establishes a pre-marketing clearance system for new

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53. *See id.*

54. *See* Coordinated Framework, supra note 8 at 23,302.

55. *See id.* at 23,303.

56. For a critique of this regulatory scheme, see Thomas O. McGarity, *Seeds of Distrust: Federal Regulation of Genetically Modified Foods*, 35 U. MICH. J. L. REFORM 403, 432-64 (2002). *See generally* Rebecca M. Bratspies, *Myths of Voluntary Compliance: Lessons from the StarLink Corn Fiasco*, 27 WM. & MARY ENVTL. L. & POL'Y REV. 593 (2003).

57. *See* Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-392 (2000). *See also* Coordinated Framework, *supra* note 8, at 23,304.

animal drugs (NAD). No NAD may be introduced into interstate commerce unless the FDA has approved the New Animal Drug Application (NADA) for that drug.[58]

The FDCA defines a new animal drug as "any drug intended for use for animals other than man, including any drug intended for use in animal feed . . . ."[59] Drugs are further defined as products "intended to affect the structure or any function of the body of man or other animals."[60] The FDA has interpreted this authority to reach transgenic fish on the theory that the transgene itself, and the protein for which it codes, affects the "structure and function" of the receiving animal in a manner analogous to that of a veterinary drug and can therefore be considered a new animal drug.[61] It is beyond dispute that in drafting the FDCA, Congress never contemplated it being applied to such a situation. Not only does the FDCA provide, at best, hazy authority for regulating animal biotechnology, but there are also serious questions about the FDA's institutional capacity to address some of the potential hazards posed by transgenic animals.[62]

A. THE FDA'S NEW ANIMAL DRUG AUTHORITY MAY NOT ENCOMPASS THE RELEVANT ENVIRONMENTAL HARMS

Promising that the public's interests will be fully protected in any decision to approve transgenic animals for general use,

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58. 21 U.S.C. § 360b(a)(1) provides:

> (1) A new animal drug shall, with respect to any particular use or intended use of such drug, be deemed unsafe for the purposes of section 351(a)(5) of this title and section 342(a)(2)(D) of this title unless—
>
> (A) there is in effect an approval of an application filed pursuant to subsection (b) of this section with respect to such use or intended use of such drug . . . .

A drug deemed unsafe under § 360b(a)(1) is considered adulterated under 21 U.S.C. § 351(a)(5), and adulterated drugs may not be introduced into interstate commerce. *See* 21 U.S.C. § 331(a).

59. *See id.* § 321(v).

60. *See id.* § 321(g)(1)(C).

61. OFFICE OF SCI. & TECH. POLICY, CASE STUDY NO. I: GROWTH-ENHANCED SALMON, CEQ/OSTP ASSESSMENT: CASE STUDIES OF ENVIRONMENTAL REGULATIONS FOR BIOTECHNOLOGY 1, 13-14 [hereinafter CEQ/OSTP Study], *available at* http://www.ostp.gov/html/ ceq_ostp_study2.pdf (last visited Mar. 19, 2005).

62. For a concerned suggestion that the FDA's current regulatory structures cannot effectively evaluate the environmental issues surrounding transgenic fish, see generally FUTURE FISH, *supra* note 29.

the federal government has assured the public that the FDA is fully prepared to regulate transgenic fish (ornamental as well as food fish) under the FDCA.[63] The government has also expressed confidence in its ability to do so in a manner that will satisfactorily protect the environment.[64]

However, the FDA's casual dismissal of the environmental concerns surrounding GloFish tells a different story, one that is perhaps understandable in light of the FDA's mandate and expertise to protect human food and drug supply but which also provides little comfort for those raising environmental concerns.[65] The FDA's authority is limited by the FDCA's express purpose to protect American consumers from the risks of *consuming* unsafe or ineffective food and drugs.[66] This purpose makes the FDCA an awkward fit for regulating *ornamental* fish like the GloFish or other "companion animals." The FDA is predominantly concerned with questions of how consumption of NADs may affect human health.[67] There is little room and even less incentive for the FDA to explore fully the many environmental concerns that might be raised by

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63. CEQ/OSTP Study, *supra* note 61, at 16. It is the Center for Veterinary Medicine that is directly responsible for regulation of animal drugs, feeds and medical devices under the FDCA. 21 U.S.C. § 301. For convenience, this article refers to the CVM and the FDA collectively as the FDA.

64. CEQ/OSTP Study, *supra* note 61, at 45. Although this study claimed that it was not a definitive policy statement that created any rights, it seems evident that this document is the definitive statement of the Executive Branch's approach to implementing the authority that Congress has delegated to it pursuant to various statutes. Just as no federal agency would view itself as free to disregard the CEQ/OSTP study in favor of a more stringent or additional regulation for transgenic animals, the FDA ought not be free to waive *sua sponte* the regulatory requirements the administration has indicated it views as binding.

65. The FDA was created in 1938 following the tragedy surrounding sulfanilamide. *See* Paul J. Quirk, *Food and Drug Administration*, *in* THE POLITICS OF REGULATION 196-97 (James Q. Wilson ed., 1980). Life saving sulfa drugs had just been discovered, and a company eager to market the drug in liquid form peddled sulfanilamide dissolved in diethylene glycol. *Id.* Unfortunately, the solvent turned out to be toxic and killed more than one hundred people. *Id.* This incident underscored the need for pre-market regulation of drugs. *Id.*; *see also* United States v. Sage Pharms, Inc., 210 F.3d 475, 479 (5th Cir. 2000) (recounting history and explaining FDCA is "designed to ensure the nation's drug supply is safe and effective.").

66. 21 U.S.C. § 360b (2000).

67. 21 C.F.R. §§ 510, 514 (2004). These sections govern new animal drugs and new animal drug applications respectively and focus much of their attention on residues in human food and threats to human health from these drugs.

transgenic ornamental fish.

Moreover, this same focus on human health that inhibits the FDA from adequately considering the problems posed by transgenic ornamental fish also poses significant barriers to the FDA's ability to regulate other transgenic animals. While the FDCA may give the FDA legal authority to regulate the food safety aspects of transgenic fish, the emerging consensus is that the bigger risk is that transgenic fish will make their way into the wild and pose a significant environmental threat.[68]

The federal government claims that, as part of its safety assessment for a new animal drug, the FDA considers "environmental effects that directly or indirectly affect the health of humans or animals."[69] Advocates of biotechnology tout a 1998 FDA guidance document,[70] directed at a wholly different set of products, as evidence that the FDA approval signifies consideration of a wide range of environmental harms including "lasting effects on ecological community dynamics" that fall within its consideration of activities that "significantly affect the quality of the human environment."[71] Unfortunately, this FDA guidance is limited to those situations in which "available data establish that there is a potential for serious harm to the environment at the expected level of exposure."[72] This guidance, even were it to apply to NADs, therefore is limited to situations in which data already exists and does not suggest that the FDA is willing to require applicants to develop such data or to investigate the possible ecological consequences of their proposed NADs.

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68. *See generally* NAT'L RESEARCH COUNCIL, *supra* note 50.

69. CEQ/OSTP Study, *supra* note 61, at 14; *see also* 21 C.F.R. 25.15(b) (directing the FDA to consider whether a proposed action may seriously affect the human environment).

70. The emphasis on this tenuously related Guidance Document is part of a coordinated strategy. For example, the identical document, 5 MYTHS ABOUT FEDERAL REGULATION OF TRANSGENIC FISH, is available verbatim from Aqua Bounty and from BIO. *See* AQUA BOUNTY TECHS., 5 MYTHS ABOUT FEDERAL REGULATION OF TRANSGENIC FISH, *available at* http://www.aquabounty.com/5myths1.html and BIOTECH. INDUS. ORG., 5 MYTHS ABOUT FEDERAL REGULATION OF TRANSGENIC FISH, *available at* http://www.bio.org//animals/salmonmyths2.asp (last visited Apr. 24, 2005). BIO is an ag-biotech lobbying group, and Aqua Bounty has a biotech company with a NAD for transgenic salmon currently before the FDA.

71. CTR. FOR BIOLOGICS EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH AND HUMAN SERVS., GUIDANCE FOR INDUSTRY: ENVIRONMENTAL ASSESSMENT OF HUMAN DRUG AND BIOLOGICS APPLICATIONS 6 (1998), *available at* http://www.fda.gov/cder/guidance/1730fnl.pdf.

72. *Id.*

Moreover, the fact that the FDA could dismiss the first transgenic animal so lightly suggests that it would be a mistake to make too much of the language in this guidance document. The government itself concedes that the FDA's authority may not extend to all environmental impacts, particularly those impacts that are mainly felt by the ecosystem itself rather than by human beings.[73] The limits inherent to the FDA's regulatory mandate raise real questions about whether the FDA has enough flexibility and expertise to address the environmental and ecological issues unique to transgenic fish. The FDA's decision not to regulate GloFish certainly does nothing to generate public confidence that the FDA is attuned to the concerns of environmental protection.

B. THE FDA'S GLOFISH DECISION DID NOT SATISFY THE FDA'S STATUTORY OBLIGATIONS UNDER THE FEDERAL FOOD DRUG AND COSMETICS ACT

Under the FDCA, the promoter of a new product must file, and the FDA must approve, a new animal drug application before a new animal drug can be sold in interstate commerce.[74] Unless this application is filed, the FDA is statutorily mandated to deem the product "unsafe"[75] and "adulterated."[76] Adulterated products may not be sold in interstate commerce.[77]

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73. CEQ/OSTP Study, *supra* note 61, at 14. The FDA clearly has some capacity to consider environmental harms. For example, in approving recombinant bovine somatotrophin, (rBST) a bovine growth hormone produced via genetically engineered bacteria, the FDA expressly considered some environmental risks that the new animal drug might pose—namely changing land use patterns, water quality, carbon dioxide emissions and syringe disposal. Stauber v. Shalala, 895 F. Supp. 1178, 1186 (W.D. Wisc. 1995); *see also* CEQ/OSTP Study, *supra* note 61, at 15 (listing other environmental risks examined in the rBST application, specifically, water quality, carbon dioxide emissions, and syringe disposal). The environmental issues considered in *Stauber* were fairly directly related to human health concerns. What is less clear is the FDA's ability to consider ecosystem harms or damage to wild species—the primary environmental concerns raised by transgenic fish. *See, e.g.*, NAT'L RESEARCH COUNCIL, *supra* note 50 at 111; FUTURE FISH, *supra* note 29, at 11-26.

74. 21 U.S.C. § 360b (2000).

75. *Id.* § 360b(a)(1) (unless a NAD application is filed, new animal drugs shall "be deemed unsafe for the purposes of section 351(a)(5)").

76. *Id.* § 351(a)(5) ("A drug or device shall be deemed to be adulterated . . . if it is a new animal drug which is unsafe within the meaning of section 360b of this title . . . .").

77. 21 U.S.C. § 331(a) in relevant part prohibits "[t]he introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded." *Id.* § 331(a). There is no denying

The Office of Science and Technology Policy (OSTP) and the Council on Environmental Quality (CEQ) expressed the Executive Branch's official intent to regulate transgenic fish, including ornamental fish, as new animal drugs.[78] It therefore came as a surprise when, in its first foray into this regulatory thicket, the FDA decided that GloFish need not comply with any of these NAD regulatory procedures.

The NAD application process is designed to force applicants to demonstrate the safety and effectiveness of new drugs before permitting the drugs to be marketed.[79] A drug is "new" if it has not been through an FDA approval process[80] and is not generally recognized as safe[81] and effective (GRAS).[82] A new drug that is not GRAS and is not the subject of an approved NAD application nor falls under an effective investigational exception is adulterated, and, if the drug is introduced into interstate commerce, criminal prosecution may result.[83] GloFish clearly qualify as an adulterated product under this standard. GloFish were not approved through either a NAD application or an effective investigational exception. Nor can GloFish qualify under the statute's definition of GRAS. Rather than apply the statutory standards, the FDA instead concluded that "[i]n the absence of a clear risk to the public health, the FDA finds no reason to regulate these particular fish."[84]

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that GloFish are currently sold in interstate commerce.

78. CEQ/OSTP Study, *supra* note 61, at 16. FDA advisory opinions and guidelines have the force of law and obligate the agency to follow them until amended or revoked. 21 C.F.R. §§ 10.85 (2004).

79. 21 U.S.C. § 360b; 21 C.F.R. § 514.1(b)(8).

80. 21 U.S.C. § 321(w).

81. *Id.* § 321(p)(2). The Act requires the FDA to consider four specific factors when assessing safety: 1) the likelihood that the drug or a substance formed in food because of the drug will be consumed; 2) the cumulative effect that the drug will be likely to have on man or other animals; 3) safety factors that experts consider appropriate for extrapolating from animal experimentation data; and 4) whether it is likely that the conditions of use proposed or suggested in the labeling will be followed. *Id.* § 360b(d)(2); 21 C.F.R. § 514.111(a)(4).

82. Effectiveness must be demonstrated on the basis of "substantial evidence" that the drug "will have the effect is purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 360b(d)(3).

83. *Id.* § 331(a).

84. *See* Glofish Statement, *supra* note 6. This decision rested primarily on a conclusion that "[b]ecause tropical aquarium fish are not used for food purposes, they pose no threat to the food supply." *Id.*

In doing so, the FDA turned the statutory burden of proof upside down. The FDCA does not require a "clear risk to public health", nor indeed any evidence of threat, to trigger regulation. On the contrary, the statute expressly requires evidence of safety before sale of a product can be approved.[85] Any drug not proven safe must be rejected and the burden of proof for demonstrating safety at all times rests squarely with the proponent of a new drug.[86] Assumptions of safety have no place in this process.

The Coordinated Framework assigns primary regulatory authority over transgenic animals to the FDA.[87] In conjunction with the CEQ and OSTP, the FDA has already declared that transgenic fish will be evaluated as new animal drugs.[88] The FDCA offers three options: a new animal drug is either 1) approved through the statutory process; 2) generally recognized as safe and effective (GRAS); or 3) an adulterated product subject to seizure.[89] The first option is clearly inapplicable as the FDA did not approve GloFish through the statutory NAD process. For the FDA to have been acting within its statutory mandate, the FDA's GloFish declaration must, therefore, have been an assertion that GloFish satisfied the second statutory option and could be considered GRAS.

C. GLOFISH CANNOT BE CONSIDERED GRAS UNDER THE FDCA

Courts have repeatedly held that a finding that a drug is "generally regarded as safe and effective," (GRAS) requires evidence of "adequate and well-controlled investigations . . . to evaluate the effectiveness of the drug involved . . . ."[90] Thus, a GRAS determination involves two steps. First, there must be a showing of an expert consensus that the product is safe and effective; and second, the expert consensus must be based on "substantial evidence" as defined in the FDCA and in FDA regulations. Such a GRAS determination must be based on

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85. *See* 21 U.S.C. § 321(w).

86. *See* 21 U.S.C. § 360b(b)(1) (listing the applicant's required disclosures to the FDA).

87. *See* Coordinated Framework, *supra* note 8, at 23,309.

88. *See supra* note 61 and accompanying text.

89. *See supra* notes 79-83 and accompanying text; 21 U.S.C. § 321(v).

90. *See* Weinberger v. Hynson, Wescott & Dunning, Inc., 412 U.S. 609, 629-30 (1972). *Weinberger* concludes that a GRAS determination must be based on the same substantial evidence standard that the FDA uses under 21 U.S.C. § 360b(d)(3) to approve a NADA. *See id.* at 613.

evidence published in the relevant scientific literature [91] and supported by a new drug application containing full reports of "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use" under the likely conditions of its use.[92] Anecdotal information (like testimony of physicians unsupported by controlled investigation or scientific publication) cannot constitute substantial evidence that a drug is GRAS.[93] Drug purveyors have unsuccessfully attempted to substitute real world experience for those regulatory factors.[94] A controlled investigation and publication of the results are explicit statutory conditions that must be met before the FDA can conclude that a drug is GRAS.

No such controlled investigation occurred with GloFish. No peer-reviewed publications support the safety of this novel organism. Although Yorktown's website does display "letters of support"[95] from reputable geneticists, these letters have not been subjected to peer review and are not the product of controlled laboratory investigation. As such, these letters are more akin to the anecdotal experience of physicians than to the kind of evidence sufficient for a GRAS determination.

Under the plain language of the statute, GloFish therefore cannot be considered GRAS. Indeed, the FDA does not make such a claim. Instead, the FDA does something far more problematic—it implies into the statute a threshold question of whether the NAD is worthy of FDCA consideration. The FDA then claims sole and unreviewable discretion to determine whether its imputed threshold has been satisfied.[96] With its

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91. *See* United States v. Pro-Ag, Inc., 796 F. Supp. 1219, 1230 (D. Minn. 1991), *aff'd*, 968 F.2d 681 (8th Cir. 1992).

92. 21 U.S.C. § 360b(d)(1)(A).

93. *See* United States v. Undetermined Quantities of Various Articles of Drug . . . Equidantin Nitrofurantoin Suspension . . . ., 675 F.2d 994, 1000 (8th Cir. 1982).

94. *See* United States v. Undetermined Quantities of Clear Plastic Bags of an Article of Drug for Veterinary Use . . . WRM-RID Dog Wormer, 963 F. Supp. 641, 645 (S.D. Ohio 1977), *aff'd*, 145 F.3d 1335 (6th Cir. 1998) (concluding that a forty-three year "track record" was not sufficient to satisfy the substantial evidence requirement for a GRAS determination).

95. *See* Glofish, Glofish Fluorescent Fish Science, *at* www.glofish.com/science.asp (last visited Mar. 21, 2005) (containing letters of support from five doctors).

96. *See* Memorandum of Law in Support of Defendant's Motion to Dismiss or, in the Alternative, for Summary Judgment at 27-29, International Tech. Ctr. v. Thompson, No. 1:04CV00062(RMU) (D.D.C. filed 2004) (giving the substance of its claim that the decision not to regulate GloFish is unreviewable), *available at* http://pacer/psc/uscourts.gov (last visited Apr. 15,

GloFish decision, the FDA ripped a large hole in the regulatory net—a hole through which all transgenic ornamental fish, and quite possibly all pets, may escape.[97] Indeed, proponents of other transgenic animals have already seized on GloFish as a precedent for how the FDA should approach non-food transgenic animals. For example, Simon Brodie, CEO of Allerca Inc. and proponent of transgenic cats and deer, has been quoted as claiming that "[a]s long as people don't start eating cats and they don't enter the food chain, then we should be handled like the GloFish."[98]

III. THE FDA DID NOT CONDUCT AN ADEQUATE ENVIRONMENTAL ASSESSMENT

The GloFish decision raises serious questions about the FDA's capacity to properly consider the environmental concerns that surround other pending applications, including those associated with transgenic salmon. The FDA's consideration of environmental safety was deeply flawed. The FDA stated that "there is no evidence" that these genetically modified fish "pose any more threat to the environment than their unmodified counterparts which have long been widely sold in the United States."[99] Ordinarily, the FDA requires the proponent of a NAD to provide evidence of environmental safety rather than staying regulatory consideration absent evidence that the NAD poses a threat to the environment. Moreover, the FDA effectively excluded ornamental fish from *any regulatory* scrutiny by drawing its authority as narrowly as possible and only covering those NADs that may pose a threat to the human

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2005).

97. For examples of genetic engineering applied to pets, see generally Doug Moe, *Madison: Cat Cloning Capital?*, CAP. TIMES, Oct. 12, 2004, *available at* http://www.madison.com/tct/opinion/column/moe/index.php?ntid=13867&ntpid=2 (last visited Mar. 21, 2005); Kristen Philipkoski, *RIP: Alba, the Glowing Bunny*, WIRED, Aug. 12, 2002, *available at* http://www.wired.com/news/medtech/0,1286,54399,00.html?tw=wn_story_related (last visited Mar. 21, 2005); Susan Rubinowitz, *Glowing Rabbit Sparks Controversy*, *available at* http://www.petplace.com/ Articles/artShow.asp?artID=1365 (last visited Mar. 21, 2005); Genetic Savings & Clone, Inc., *Missy: Our Inspiration*, *available at* http://www.savingsandclone.com/about_us/ missy.html (last visited Mar. 21, 2005).

98. *See* Elias, *supra* note 12.

99. Glofish Statement. *supra* note 6.

food supply.[100] Such an interpretation not only unduly limits the FDA's authority under the FDCA, it also flatly contradicts the FDA's duties under the National Environmental Policy Act (NEPA).[101]

A. THE FDA FAILED TO COMPLY WITH NEPA

NEPA's central statutory purpose is to prevent agencies from disregarding environmental issues out of hand.[102] To that end, NEPA regulations ensure that an agency takes a "hard look" at the effects of its actions.[103] Section 1502.1 of the Code of Federal Regulations articulates this purpose with great particularity, establishing that the statement is meant "to serve as an action-forcing device to ensure that the [environmental] policies and goals defined in the Act are infused into the ongoing programs and actions of the Federal Government."[104] Agencies are compelled to collect and disseminate information about the environmental consequences of proposed actions that fall under their respective jurisdictions.[105] Similarly, the broad dissemination of information mandated by NEPA permits the public and other

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100. In a lawsuit challenging this FDA decision not to regulate GloFish, the International Center for Technology Assessment and the Center for Food Safety have asserted that even under this narrow vision of its authority, the FDA had both the authority and a duty to regulate GloFish. *See* Complaint, Int'l Ctr. for Tech. Assessment v. Thompson, No. 1:04CV00062 (D.D.C. filed Jan. 1, 2004), *available at* http://64.78.7.168/pubs/GloFishComplaint1.14.2004.pdf (last visited Mar. 22, 2005) [hereinafter Thompson Complaint]; Defendants' Motion to Dismiss or, In the Alternative, for Summary Judgment, Int'l Ctr. for Tech. Assessment v. Thompson, No. 1:04CV0006 (D.D.C. filed April 19, 2004), *available at* http://www.Ecf.dcd.uscourts.gov [hereinafter Defendants' Motion].

101. *See generally* National Environmental Policy Act (NEPA), 42 U.S.C. § 4321-4370(f) (2000).

102. *See* 42 U.S.C. § 4321; Marsh v. Oregon Natural Res. Council, 490 U.S. 360, 371 (1989) ("NEPA promotes its sweeping commitment to 'prevent or eliminate damage to the environment and biosphere' by focusing Government and public attention on the environmental effects of proposed agency action.")

103. *See* Kleppe v. Sierra Club, 427 U.S. 390, 410 n.21 (1976); *see also* 42 U.S.C. § 4321 (identifying NEPA purposes as including "[t]o declare a national policy which will encourage productive and enjoyable harmony between man and his environment; to promote efforts which will prevent or eliminate damage to the environment and biosphere . . . to enrich the understanding of the ecological systems and natural resources important to the Nation . . . ."). For an interesting critique of NEPA, see generally Bradley C. Karkkainen, *Whither NEPA?*, 12 N.Y.U. ENVTL. L.J. 333 (2004).

104. 40 C.F.R. § 1502.1 (2004).

105. *See id.* § 1502.1; 42 U.S.C. § 4332.

government agencies to react to the effects of a proposed action at a meaningful time.[106]

To achieve these ends, NEPA requires agencies to conduct environmental reviews on all "major Federal actions significantly affecting the quality of the human environment."[107] NEPA's implementing regulations define a "major federal action" as an action to include those actions whose effects "may be major,"[108] and to cover any "circumstance where the responsible officials fail to act."[109] NEPA's implementing regulations further define "effects" and "impacts" to be synonymous and both terms are interpreted broadly to include federal actions raising "ecological . . . aesthetic, historic, cultural, economic, social, or health [concerns] whether direct, indirect, or cumulative."[110]

Agencies use the Environmental Impact Statement (EIS) process to implement this environmental review requirement. Each EIS must include "any adverse environmental effects which cannot be avoided should the proposal be implemented,"[111] and NEPA regulations direct agencies to use their best efforts to "avoid or minimize any possible adverse effects"[112] and to explore alternatives "that will avoid or minimize adverse effects."[113]

Twenty years ago, the D.C. Circuit enjoined the National Institute of Health (NIH) from approving the deliberate release of genetically engineered organisms without first conducting an

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106. *See* 40 C.F.R. § 1502.5 (establishing the timing requirements for environmental impact statements and emphasizing that the "statement should be prepared early enough so that it can serve practically as an important contribution to the decisionmaking process and will not be used to rationalize or justify decisions already made.").

107. 42 U.S.C. § 4332(2)(C).

108. *See* Public Citizen v. Dep't of Transp., 316 F.3d 1002, 1022 (9th Cir. 2003) (quoting 40 C.F.R. § 1508.18). A coalition of consumer groups sued the FDA on January 14, 2004, challenging the agency's GloFish decision as a failure to regulate. In its filings in this litigation, the FDA has defended its actions by asserting that its GloFish decision was not an agency action, and/or was not a major federal action. *See* Defendants' Motion, *supra* note 100. The circularity of this claim is striking. Approval of a NAD is clearly a federal action triggering NEPA review. CEQ/OSTP Study, *supra* note 61, at 14. The FDA used substantial equivalence to conclude that a NAD was unnecessary, and then bootstrapped the lack of a NAD as grounds not to invoke NEPA.

109. 40 C.F.R. § 1508.18.

110. *Id.* § 1508.8.

111. 42 U.S.C. § 4332(2)(C)(ii).

112. 40 C.F.R. § 1500.2(f).

113. *Id.* §1500.2(e).

environmental assessment.[114] The NIH had approved the deliberate release of ice-minus bacteria without conducting an environmental assessment or an environmental impact analysis under NEPA. Writing for the majority, Judge J. Skelly Wright concluded that the NIH has failed to display "the rigorous attention to environmental concerns demanded by law."[115] He pointed out that NEPA would be toothless if agencies could satisfy their NEPA obligations merely by issuing conclusory statements that actions producing significant changes of the status quo, like the first deliberate release of a genetically modified organism, would have no environmental impacts.[116] Reading NEPA as the product of a special congressional concern with the effects of new technology on the environment,[117] the concurring opinion reasoned that release of genetically engineered organisms needed a level of scrutiny sufficient both to ensure safety and to reassure the public.[118] Although NEPA has been reinterpreted over the years, this basic core remains.

The FDA's announcement that it would not regulate GloFish unleashed the first commercial distribution of a transgenic animal in the United States and raises eerie parallels to the NIH's earlier attempt to permit the ice-minus experiment with no assessment of environmental risks. The FDA's decision not to regulate (and therefore to permit marketing of GloFish) was not based *on any* environmental risk assessment process. The FDA conducted no EIS, produced no Environmental Assessment (EA),[119] and made no findings that

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114. *See* Foundation on Econ. Trends v. Heckler, 756 F.2d 143, 146 (D.C. Cir. 1985).

115. *Id.* at 146.

116. *Id.*

117. *Id.* at 147. The court noted that NEPA explicitly enumerates "new and expanding technological advances" as one of the activities with the potential to threaten the environment. *Id.* (quoting 42 U.S.C. §4331(a) (2000)). The court further emphasized that the legislative history reveals a concern with "[a] growing technological power . . . far outstripping man's capacity to understand and ability to control its impact on the environment." *Id.* (quoting S. Rep. No. 91-296 at 6, (1969)).

118. *See id.* at 161 (MacKinnon, J., concurring).

119. Under NEPA, an initial EA is used to determine if an in depth EIS is needed. *See* 40 C.F.R. § 1501.4(C) (2004). If required, an EIS examines the long and short-term environmental effects from the proposed action and alternative actions that could be taken. *See id.* § 1502.1. Although NEPA imposes no substantive burden on agency decision making, it does require procedural protections chiefly intended to prevent agencies from ignoring environmental concerns in their decision making. *See generally id.* § 1502.

GloFish were likely to have no significant impact (FONSI).[120] In short, none of the investigative and contemplative steps required under NEPA were performed and no governmental agency considered whether unregulated sale of GloFish would have negative environmental impacts.

This failure is particularly troubling because commercial production of these fish will inevitably lead to release of some proportion of these fish into the wild.[121] Indeed, dumping of unwanted aquarium fish and plants is a primary source of invasive species. The FDA's three sentence opinion plainly dismissed out of hand all the complex questions surrounding this kind of intentional release. While many aquarium fish, or ornamentals, do not survive in the waters of the United States,[122] there are, unfortunately, ample examples of such fish not only surviving but reproducing and competing with native species.[123]

Here the FDA seems to have undercut NEPA by operating on a "no news is good news" principle.

120. By contrast, Canadian authorities have seized GloFish, classifying them as illegal because the fish have not gone through an environmental risk assessment. *See* Leanne Dohy & Hanneke Brooymans, *GloFish Sales Halted By Feds: Genetically Modified Species Raises Health Fears*, CALGARY HERALD, Feb. 15 2004, at A11. Somewhat ironically, Singapore Agri-Food and Veterinary authorities have seized Glofish imported from Taiwan. *See* Chang Ai-Lien, *NUS Glofish To Be Sold in the US . . . But Not Here*, STRAITS TIMES, Dec. 10, 2003. The fish developed by a Singapore laboratory are not approved for sale in Singapore and importers are threatened with jail terms and thousands of dollars in fines. *Id.*

121. *See* Press Release, U.S. Geological Survey, U.S. Dep't of the Interior, *Got Fish? Already Tired of that Holiday Gift Aquarium? Think Before You Dump and Create an Even Bigger Problem* (Jan. 25, 2001), *available at* http://www.usgs.gov/public/press/ public_affairs/press_releases/pr1381m.html (last visited Mar. 22, 2005). *See generally* U.S. GEOLOGICAL SURVEY, U.S. DEPT. OF THE INTERIOR, NON-INDIGENOUS AQUATIC SPECIES DATABASE, *available at* http://nas.er.usgs.gov/default.asp (last visited Mar. 22, 2005).

122. *See* Stephen Hsu, *Taikong Corporation Leader in Marine Biotechnology*, TAIWAN NEWS, Sept. 28, 2004, *available at* 2004 WLNR 7441444.

123. CEQ/OSTP Study, *supra* note 61, at 42 (acknowledging that intentional and unintentional release of non-native aquarium fish have already led to severe environmental problems in the United States, with nearly 150 exotic ornamental fish found in the wild in the United States); *see also* Letter from American Ecosystem and Exotic Species Research Scientists, Attachment: Nonindigenous Organisms in the Aquarium Industry that Have Been Released into U.S. Waters, to Secretary of Interior Bruce Babbitt (Oct. 19, 1998) (on file with author) (regarding invasive species and characterizing zebra danao as "established in the wild in the United States outside its native range"); Dianna K. Padilla & Susan L. Williams, *Beyond Ballast Water: Aquarium and Ornamental Trades as Sources of Invasive Species in Aquatic*

At the time of this writing, no permanent zebrafish populations exist in United States waters. However, invasive populations of zebrafish have been documented in California, Florida, New Mexico, and Connecticut.[124] In all cases, the invasive species were traced back either to aquarium releases or to escapes from commercial fish breeding sites.[125] There is certainly no reason to believe that GloFish would escape or be dumped less often than their unmodified kin.[126] Moreover, since some purveyors claim that transgenic zebrafish can survive in waters much colder than those in which zebrafish are usually found, there is no assurance that genetically modified zebrafish could not survive in American waters.[127] Yorktown admits that its GloFish are fully fertile, and indeed, at least one homebreeder has succeeded in not only breeding GloFish but also in crossing GloFish with other kinds of zebrafish.[128]

Complex as this question is in the United States, it pales in comparison to the possible risks when aquarium fish are sold in their center of origin. Zebrafish, for example, are native to the Indian subcontinent.[129] The aquarium trade is an

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Ecosystems, 2 FRONTIERS IN ECOLOGY & ENV'T, 131-38 (Apr. 2004) (concluding that one-third of the world's worst invasive species are ornamental aquarium species).

124. Leo Nico & Pam Fuller, *Brachydanio rerio*, *in* NONINDIGENOUS AQUATIC SPECIES DATABASE (revised July 22, 2003), *at* http://nas.er.usgs.gov/queries/FactSheet.asp?speciesID=505; *see also* Decl. of Susan L. Williams at 2-3, Int'l Ctr. for Tech. Assessment v. Thompson, No. 1:04CV00062 (D.D.C. 2004) [hereinafter Williams Decl.], *available at* http://pacer/psc/uscourts.gov (last visited Apr. 24, 2005).

125. *See* Williams Decl., *supra* note 124, at 2.

126. Zebrafish are a popular research species for genetic engineering, making this question a pressing one. For example, researchers have recent demonstrated the possibility of producing human coagulation factor VII in zebra danios and tilapia. *See generally* Gyulin Hwang et al., *Fish as Bioreactors: Transgene Expression of Human Coagulation Factor VII in Fish Embryos*, MARINE BIOTECH., Oct., 2004, *available at* http://springerlink.metapress.com/ (last visited Jan. 31, 2005).

127. *See* Hsu, *supra* note 122. Unlike Yorktown, Taikong claims to sterilize ninety percent of its transgenic fish—a rate that it describes as "good enough." Needless to say, this assessment of safety is strongly challenged by opponents of the technology.

128. *See PFK Reader Breeds GM Fish*, PRACTICAL FISH KEEPING, Mar. 2, 2004, *available at* http://www.practicalfishkeeping.co.uk/pfk/pages/item.php?news=220 (last visited Apr. 22, 2005).

129. Zebrafish Info. Network, Univ. of Or. Inst. of Neuroscience, Zebrafish K-12, Zebrafish FAQs, *available at*

international one, and the FDA's actions make it likely that these fish will be sold into their center of origin in the relatively near future. If the FDA, the agency charged with regulating these transgenic fish does not consider this point, will anyone?

Even though release or escape of GloFish into the wild might have significant ecological impacts, nobody has evaluated these impacts. With this decision, the FDA has loosed into the metaphorical streams of commerce a transgenic, highly mobile organism with no consideration of the likely environmental effects the fish will have on the actual streams of the nation. And, as GloFish pass through the stream of commerce, these fish will inevitably enter the nation's streams and waters. One expert characterizes the situation as one in which regulators were "caught unaware by [the GloFish] . . . and it went forward and went commercial very quickly."[130]

The FDA's NEPA regulations are drafted extremely narrowly. The FDA does not require its scientists to consult with experts from other agencies and FDA scientists, though highly skilled, are not experts in population biology or ecology—the disciplines raising the biggest questions about transgenic fish. Even more troubling, the FDA's regulations categorically exclude from NEPA assessment all NAD applications for drugs intended for use in nonfood animals.[131] There might be some comfort in the fact that this categorical exclusion does not apply under exceptional circumstances,[132] but concerns remain. The FDA's casual dismissal of the unknowns swirling around GloFish suggests that the FDA's interpretation of "exceptional circumstances" is likely to be very narrow.[133]

The fact that the FDA did not invoke this categorical NEPA exemption for GloFish provides only cold comfort. First, the FDA's decision that GloFish need not be subject to the

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http://www.neuro.uoregon.edu/k12/FAQs.html (last visited Apr. 22, 2005).

130. Gregory Lamb, *Glofish Zoom to Market*, CHRISTIAN SCI. MONITOR, Jan. 22, 2004 (quoting Eric Hallerman, Professor of Fisheries and Wildlife Science, Virginia Tech University), *at* http://www.csmonitor.com/2004/0122/p14s02-sten.html (last visited Apr. 24, 2005).

131. 21 C.F.R. § 25.33(d)(1) (2004).

132. *Id.* § 25.15(d).

133. The FDA's general NEPA regulations require that any application for a categorical exemption, like that for non-food animals, must be accompanied by a statement that "to the applicant's knowledge, no extraordinary circumstances exist." *Id.* § 25.15(a).

FDA's regulatory authority is in many ways even more troubling. Second, the FDA's language in dismissing GloFish, with its clear emphasis on human health, suggests that the FDA is unlikely to explore these environmental questions fully or to engage in any effective NEPA analysis of transgenic aquarium fish or other non-food transgenic animals.[134] Thus, some of the most serious potential impacts of transgenic animals[135]—including harm to wild populations through competition or erosion of genetic diversity with the attendant decrease in community resilience—would appear to fall outside the government's own characterization of its authority. This is the result despite a growing body of scientific evidence suggesting that transgenic animals could involve dimensions of risk not present for unmodified animals.[136] Responsible regulatory oversight must consider the environmental effects of transgenic animals, including released transgenic ornamental fish before any more such fish are sold in the aquarium trade.[137]

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134. The FDA is already under fire for routinely ignoring the environmental effects of persistent pharmacological compounds in the environment. *See* Andrew C. Revkin, *F.D.A. Considers New Tests for Environmental Effects*, N.Y. TIMES, Mar. 14, 2002, at A20. *See generally* Dana W. Kolpin et al., *Pharmaceuticals, Hormones and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance*, 36 ENVTL. SCI. & TECH. 1202 (2002) (demonstrating the environmental effects).

135. Serious concerns also surround transgenic animals, including questions of whether these animals can safely be part of the food chain and whether genetic manipulations are fair to the animals themselves. That said, the most immediate worries are environmental. *See, e.g.*, James Gorman, *When Fish Flouresce, Can Teenagers Be Far Behind?*, N.Y. TIMES, Dec. 2, 2003, at F3; Andrew Pollack, *Gene-Altering Revolution Is About to Reach the Local Pet Store: Glo- n-the-Dark Fish*, N.Y. TIMES, Nov. 22, 2003, at A12; *see also* NAT'L RESEARCH COUNCIL, BIOLOGICAL CONFINEMENT OF GENETICALLY ENGINEERED ORGANISMS 48 (2004), *available at* http://www.nap.edu/books/0309090857/html/ (last visited Apr. 10, 2005).

136. *See, e.g.*, W.M. Muir & R.D. Howard, *Fitness Components and Ecological Risk of Transgenic Release: A Model Using Japanese Medaka*, 158 AM. NATURALIST, 1 (2001); W.M. Muir & R.D. Howard, *Possible Ecological Risks of Transgenic Organism Release When Transgenes Affect Mating Success: Sexual Selection and the Trojan Gene Hypothesis*, 96 PROC. NAT'L. ACAD. SCI. 13,853-56 (Nov. 23, 1999) [hereinafter Muir & Howard, *Possible Ecological Risks*].

137. Indeed, under Executive Order 13,112, each federal agency is required:

> 3) not authorize, fund, or carry out actions that it believes are likely to cause or promote the introduction or spread of invasive species in the United States or elsewhere unless, pursuant to guidelines that it has prescribed, the agency has determined and made public its

IV. THE COORDINATED FRAMEWORK VERSUS STATUTORY MANDATES

When regulating biotech food crops, the FDA treats genetically modified foods as "substantially equivalent" to their conventional counterparts.[138] Substantial equivalence is a term from the Coordinated Framework[139]—the Executive Branch policy document generated in the mid-1980s.[140] Pursuant to the Coordinated Framework, the FDA presumes the safety of novel chimeric foods and regulates only if there is evidence that a genetically modified food produces a risk different from those posed by its unmodified cousins.[141] The FDA's failure to fulfill its statutory mandates with regard to transgenic fish grows from a misapplication of this same notion of substantial equivalence. Indeed, misplaced notions of substantial equivalence ring out loudly from the FDA's statement that: "[t]here is no evidence that these genetically engineered zebra danio fish pose any more threat to the environment than their unmodified counterparts which have long been widely sold in the United States."[142]

In drafting the Coordinated Framework, the Reagan Administration considered whether new statutory authority would be necessary to respond to the challenges posed by developments in molecular biology.[143] The Administration concluded that existing authority could adequately protect the public from harm from these new technological developments.[144] The Coordinated Framework thus represents

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> determination that the benefits of such actions clearly outweigh the potential harm caused by invasive species; and that all feasible and prudent measures to minimize risk of harm will be taken in conjunction with the actions.

Exec. Order No. 13,112, 64 Fed. Reg. 6,183-84 (February 3, 1999). Needless to say, the FDA has neither determined nor made public any such analysis.

138. Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. 22,984, 22,985 (May 29, 1992). *See also* Draft Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Biotechnology, 66 Fed. Reg. 4839-42 (Jan 18, 2001). For an interesting insider perspective that is critical of the Coordinated Framework, see Sen. Al Gore, *Planning a New Biotech Policy*, 5 HARV. J. L & TECH. 19 (1991).

139. *See generally* Coordinated Framework, *supra* note 8.

140. *Id.* at 22,302.

141. *Id.*

142. *See* Glofish Statement, *supra* note 6.

143. *See* Coordinated Framework, *supra* note 8, at 23,302-03.

144. *See id.*

an Executive Branch policy of treating the products of new techniques for genetic modification as the "substantial equivalents" of their unmodified counterparts. As the "substantial equivalents" of conventional products, the fruits of genetic engineering needed no special regulatory regime. Thus, "substantial equivalence" became the touchstone for integrating evaluation of genetically modified products—plants, animals, and microbes—into a matrix of pre-existing regulatory statutes.

In its GloFish decision, the FDA proceeded squarely within this "substantial equivalence" paradigm. The products of biotechnology and genetic engineering are presumed to be safe, and the burden of proof rests with anyone desiring to challenge that presumption. Unfortunately, this deferential substantial equivalence vision of regulation conflicts head on with the kind of assessment the FDA is required to perform under the FDCA. Because the FDA's GloFish decision had the effect of introducing a new animal drug into interstate commerce, it is reviewable under the federal law,[145] just like all other FDA decisions to permit NADs to enter interstate commerce. Although the standard of review is deferential, an agency decision may be set aside if it is arbitrary and capricious, an abuse of discretion, or otherwise not in accordance with the law.[146] In announcing that it would not regulate GloFish, the FDA implicated all of these grounds.

A. SUBSTANTIAL EQUIVALENCE UNDERMINES THE FDA'S ABILITY TO REGULATE TRANSGENIC ANIMALS UNDER THE NEW ANIMAL DRUG ACT

A close look at the language the FDA used in its declaration raises warning flags that the FDA discarded the relevant statutory factors, and replaced them with the principle of substantial equivalence articulated in the Coordinated Framework. Such an application is misplaced. The FDA has already announced that transgenic animals contain new animal drugs that must be regulated in accordance with the FDCA. These animals are thus inherently different from, rather than the "substantial equivalent" of unmodified animals that do not contain new animal drugs and are, therefore, not subject to

145. *See* 5 U.S.C. § 801 (2004); *see also id.* §§ 551-59, 701-06.

146. Upjohn Mfg. Co. v. Schweiker, 681 F.2d 480, 483 (6th Cir. 1982); *see also* 5 U.S.C. § 706(2)(A).

that portion of the FDCA.

Resort to substantial equivalence is entirely inappropriate for assessing the safety of new animal drugs. As explained earlier, the FDCA does not give the FDA authority to grant waivers from the NAD process, unless the drug is GRAS.[147] The GRAS process is very specific—little is left to agency discretion. The FDA deviated from these statutorily prescribed processes for evaluating new drugs, and instead applied the Framework's notion of "substantial equivalence." This "substantial equivalence" approach led the FDA to substitute assumptions of equivalence for statutorily-mandated proof that the transgenic fish is generally regarded as safe and effective.[148]

Rather than applying its statutory authority as delegated, the FDA, in effect, created an additional threshold question: whether the NAD is the "substantial equivalent" of its unmodified counterpart. The FDA thus assumed for itself the power to grant waivers from the NAD process whenever it concluded that "substantial equivalence" has been satisfied. Since under the Coordinated Framework, the FDA is already committed to the conclusion that the products of genetic engineering will be the "substantial equivalent" of their unmodified counterparts,[149] this imputed threshold question may well eviscerate the FDA's statutory duty to regulate NADs under the FDCA.

At the very least, applying a "substantial equivalence" standard to GloFish involved unacceptably shifting the burden

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147. For a vigorous academic analysis of the limits on waivers in an administrative system, see Jim Rossi, *Making Policy Through the Waiver of Regulations at the Federal Energy Regulatory Commission*, 47 ADMIN. L. REV. 255, 277-78 (1995); Peter H. Schuck, *When the Exception Becomes the Rule: Regulatory Equity and the Formulation of Energy Policy Through an Exceptions Process*, 1984 DUKE L.J. 163 (1984); Alfred C. Aman, Jr., *Administrative Equity: An Analysis of Exceptions to Administrative Rules*, 1982 DUKE L.J. 277 (1982).

148. *See, e.g.*, Motor Vehicles Mfrs. Ass'n v. State Farm Mut. Ins. Co., 463 U.S. 29, 43 (1983) (stating that agency action will be improper if the agency relies on factors which "Congress has not intended it to consider" and fails to consider statutory factors); Oregon v. Ashcroft, 368 F.3d 1118 (9th Cir. 2004) (concluding that the Attorney General exceeded his statutory authority when he failed to consider statutorily required factors before issuing a directive); Independent U.S. Tanker Owners Comm. v. Dole, 809 F.2d 847 (D.C. Cir. 1987) (reversing agency decision because court concluded that administrator had permitted the administration's policies to supplant statutorily identified objectives for decision making).

149. *See* Coordinated Framework, *supra* note 8, at 22,302.

of proof from the purveyor of a NAD to prove safety to those objecting to the drug to demonstrate danger. In drafting the FDCA, Congress created a presumption against marketing or sale of a product, unless the product's proponent demonstrated a requisite level of safety is demonstrated.[150] The FDA seems to have used "substantial equivalence" to stand this legislatively-imposed burden of proof on its head.

Where the statute declares anything not proven safe to be adulterated and therefore illegal, the FDA announced that it would regulate GloFish only if presented with evidence of harm. In doing so, the FDA contradicted its public pronouncements that transgenic animals would be regulated as NADs, and instead claimed a hidden, case-by-case discretion to determine whether a transgenic animal qualifies as a new animal drug. The GloFish decision thus replaced the NAD default that marketing of a product be permitted only after safety has been demonstrated with the Coordinated Framework's presumption in favor of marketing the products of biotechnology in the absence of evidence of unique dangers.

B. SUBSTANTIAL EQUIVALENCE UNDERMINES THE FDA'S ABILITY TO CONDUCT A NEPA ANALYSIS

Like other federal agencies, the FDA has duties under NEPA to ensure that its "policies and programs will be planned, developed, and implemented to achieve the policies declared by NEPA and required by the CEQ's regulations to ensure responsible stewardship of the environment for present and future generations."[151] The FDA's use of "substantial equivalence" as a reason not to engage in a NEPA analysis of GloFish raises serious concerns about how the FDA will approach the environmental effects of transgenic fish that do not qualify for the categorical exclusion. The FDA's NEPA regulations make it clear that the FDA need not duplicate its efforts by re-analyzing under NEPA factors that were already considered under the NAD. With regard to transgenic fish, however, there are likely to be significant environmental issues

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150. The FDCA places the responsibility squarely on the sponsor of a drug to demonstrate that drug's safety, and directs the FDA to approve for marketing only those drugs whose safety has been demonstrated. *See* 21 U.S.C. § 355(b)(1) (2000). This allocation of responsibility ensures that any significant uncertainty about safety or effectiveness is to be borne by a drug's sponsor not its consumer.

151. 21 C.F.R. § 25.10(a) (2004).

not encompassed by a NAD evaluation.

Rather than engage in the proper NEPA process, the FDA relied on "substantial equivalence" to conclude that its actions fell outside the scope of NEPA. With no evaluation of the likely or possible environmental effects attendant on sale of GloFish, the FDA merely assumed that transgenic fish are the "substantial equivalent" of conventional zebrafish, and then further assumed that this substantial equivalence meant that GloFish posed no risk to the environment. These assumptions fly in the face of a significant body of scientific scholarship detailing the various behavioral and survival differences between conventional fish and their genetically altered counterparts[152] and do not account for claims that transgenic zebrafish can survive under a broader range of temperature conditions than their unmodified counterparts. In relying on "substantial equivalence," the FDA also ignored significant regulatory concerns identified by the National Research Council[153] and by the FDA itself when it initially asserted this authority.[154]

C. SUBSTANTIAL EQUIVALENCE RAISES SEPARATION OF POWERS CONCERNS

The FDA's GloFish decision represents a serious departure from the generally accepted structure of constitutional action for co-equal branches of government. The FDA impermissibly replaced its NAD statutorily-mandated decisional matrix with an executive policy position. Agencies cannot overrule Congress by administrative fiat.[155] An agency is entitled to make decisions based on its view of wise policy but only within

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152. *See generally* R.H. Devlin et al., *Increased Ability to Compete for Food by Growth Hormone-Transgenic Coho Salmon* Oncorhynchus kisutch *(Walbaum)*, 30 AQUACULTURE RES. 479 (1999); José de la Fuente et al., *Growth Regulation and Enhancement in Tilapia: Basic Research Findings and Their Applications*, 15 GENETIC ANALYSIS 85 (1999); Anne R. Kapuscinski & Eric M. Hallerman, *Implications of Introduction of Transgenic Fish into Natural Ecosystems*, 48 CAN. J. FISHERIES & AQUATIC SCI. 99 (1991); William M. Muir & Richard D. Howard, *Assessment of Possible Ecological Risks and Hazards of Transgenic Fish with Implications for Other Sexually Reproducing Organisms*, 11 TRANSGENIC RES. 101 (2002).

153. NAT'L RESEARCH COUNCIL, *supra* note 50, at 108-21.

154. CEQ/OSTP Study, *supra* note 61, at 21.

155. For a speech by then Assistant General Counsel of the FDA making this point, see Peter Barton Hutt, *Philosophy of Regulation Under the Federal Food, Drug and Cosmetic Act*, FOOD DRUG COSMETIC L.J. 177, 179 (1973).

the parameters of the authority delegated to it by Congress.[156] Importing the Coordinated Framework's already problematic concept of "substantial equivalence" into the GloFish decision undermines the statutory foundation upon which the administrative policy of substantial equivalence was built.[157]

An administrative policy intended to direct evaluation of GM products into an existing statutory rubric instead became a means for avoiding application of that very same statutory rubric. By shifting primary lawmaking authority from Congress to the Executive Branch, this use of the Coordinated Framework circumvents the FDA's statutorily created mandates and abrogates critical limitations on the scope of the FDA's delegated authority under both FDCA and NEPA.

Using executive policy to trump not one, but two statutory mandates implicates significant separation of powers concerns. Coupled with the executive's assertion that its GloFish decision is entirely unreviewable, the consequences would be the Executive Branch creating, implementing, and reviewing its own authority with no input or constraints from the co-equal branches of government. With this decision, the potential for arbitrary agency behavior has skyrocketed, and unfortunately so has the likelihood of irreversible environmental harm.

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156. Even *Heckler v. Chaney*, which in many ways represented the high point for court findings that agency decisions were unreviewable, clearly intended that agency discretion be limited by the statutory mandate. Heckler v. Chaney, 470 U.S. 821, 833 n.4 (1985). *See also* Ronald M. Levin, *Understanding Unreviewability in Administrative Law*, 74 MINN. L. REV. 689, 752-62 (1990).

157. *See, e.g.*, Bowen v. Georgetown Univ. Hosp. 488 U.S. 204 (1988) (agency power is limited to the authority delegated by Congress and regulations must be issued within the power conferred by the legislature); Federal Mar. Comm'n v. Anglo-Canadian Shipping Co., 335 F.2d 255, 258 (9th Cir. 1964) (agency freedom to regulate is limited by the Congressional intent expressed in the agency's enabling statute).

V. THE ELEPHANT IN THE ROOM: ENVIRONMENTAL RISKS POSED BY AQUACULTURE[158] OF TRANSGENIC SALMON

The FDA's GloFish decision calls into question both the scope of the FDA's authority to consider ecological impacts of transgenic salmon and its willingness to exert whatever authority it might possess. Regardless of the dubious merits of the FDA's NEPA and NAD assertions with regard to GloFish, it is clear that approval of transgenic salmon, or the approval of other transgenic food animals, would be a major federal action subject to NEPA and require a NAD. While this technology seems to hold tremendous promise, it cries out for a regulatory scheme to maximize the likelihood that transgenic fish are raised and marketed in a fashion that protects public welfare. The FDA's disregard, in the context of GloFish, of the very environmental considerations that will be raised by commercial aquaculture of transgenic salmon does not engender confidence that the FDA is willing to engage in the necessary inquiry. As a result, there is a significant possibility that important environmental concerns will not find their way into the regulatory decision making process. Meanwhile, commercial pressures on the FDA to approve transgenic fish are mounting.

A. SOME DETAILS OF AQUA BOUNTY'S TRANSGENIC SALMON

The FDA is currently considering an application submitted by Aqua Bounty Farms[159] for what would be the first permit to grow a transgenic animal commercially for food.[160] Aqua

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158. There is a large and growing body of scholarship documenting the adverse environmental effects of aquaculture generally. That topic is beyond the scope of this article which focuses on the unique environmental challenges posed by aquaculture of transgenic fish. Readers interested in aquaculture more generally should see Rosamond L. Naylor et al., *Effects of Aquaculture on World Fish Supplies*, 405 NATURE 1017 (2000); FAO Fisheries Dep't, *Review of the State of World Aquaculture*, FAO FISHERIES CIRCULAR No. 886 (1997), *available at* http:www.fao.org/docrep/003/w7499e/ w7499e00.htm (last visited Apr. 10, 2005); MICHAEL L. WEBER, SEAWEB AQUACULTURE CLEARINGHOUSE, WHAT PRICED FARMED FISH: A REVIEW OF THE ENVIRONMENTAL AND SOCIAL COSTS OF FARMING CARNIVOROUS FISH (2003), *available at* http://www.seaweb.org/resources/sac/pdf/WhatPriceFarmedFish_high.pdf.

159. The firm is now known as Aqua Bounty Technologies, Inc.

160. The FDA has not posted the application, nor has it been published in the federal register. That said, Aqua Bounty officials talk freely about their application and their hopes for the transgenic salmon they call AquAdvantage. *See, e.g.*, PEW INITIATIVE ON FOOD AND BIOTECHNOLOGY, ONE FISH, TWO FISH, GENETICALLY NEW FISH (Nov. 13, 2003), *available at*

Bounty has requested that its transgenic salmon be approved under the same NAD authority putatively exercised in the FDA's decision not to regulate GloFish. Aqua Bounty genetically modifies its salmon by microinjecting a transgene construct consisting of an ocean pout AFP promoter linked to a chinhook salmon GH cDNA.[161] This transgene construct enables the fish to produce growth hormone year round, rather than only during the spring and summer. As a result, Aqua Bounty's transgenic fish should increase in weight up to six times faster than nontransgenic salmon.[162] The company acknowledges that escaped transgenic fish may pose significant risks to wild salmon populations and more generally that sea pen aquaculture is associated with negative environmental consequences.[163] Aqua Bounty has spent years working with regulators and with the concerned public to confront these challenges in a way that makes commercial and environmental sense.

But for Aqua Bounty's voluntary public disclosure of its application, however, the Trade Secrets Act[164] would have prevented any public participation in the decision making process.[165] The Trade Secrets Act similarly prevents the FDA from discussing whether any other applications have been filed for approval of other transgenic fish.[166] As a result, the public

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http://pewagbiotech.org/newsroom/summaries/ display.php3?NewsID=543; Bettina Metzler, Mathias Schmidt, and Eckhard Stein, eds., Commercialization of Path-Breaking Transgenic Salmon Faces Stumbling Blocks (Apr. 5, 2000), *available at* http://www.netlink.de/gen/Zeitung/2000/000405h.html (last visited Apr. 22, 2005); *see also* CEQ/OSTP Study, *supra* note 61; Carol Kaesuk Yoon, *Altered Salmon Leading Way to Dinner Plates, but Rules Lag,* N.Y. TIMES, May 1, 2000, at A1; UNION OF CONCERNED SCIENTISTS, GENETICALLY ENGINEERED SALMON (Feb. 1, 2001), *available at* http://www.ucsusa.org/food_and_environment/biotechnology/page.cfm?pageID=327 (last modified July 18, 2003).

161. Erik Stokstad, *Engineered Fish: Friend or Foe of the Environment?*, 297 SCIENCE 1797, 1797 (2002).

162. *Id.* at 1799.

163. G.L. Fletcher et al, *Current Status of Transgenic Atlantic Salmon for Aquaculture*, in PROCEEDINGS OF 6TH INTERNATIONAL SYMPOSIUM ON THE BIOSAFETY OF GENETICALLY MODIFIED ORGANISMS, *available at* http://www.aquabounty.com/abbounty.htm (last visited April 10, 2005).

164. 18 U.S.C. § 1905 (2000). The Trade Secrets Act requires that the FDA keep secret all of the investigations and pre-market notifications that precede the release of a new animal drug, including whether or not any such petition exists. *Id.*

165. *See* 18 U.S.C. § 1905 (2000).

166. *Id.*

has no idea how many applications for transgenic animals are pending. The National Research Council has expressed its serious concern about the consequences of excluding the public from this process, [167] particularly in light of the explicit provisions for transparency and public participation in NEPA's environmental assessment process.[168]

Aqua Bounty has voluntarily provided the information that it has submitted many of the scientific reports required for a NAD approval.[169] The company deserves credit for its willingness to provide the public this information that it could legally keep secret. However, depending on the kindness of strangers, so to speak, is no way to build a regulatory system. The FDA acknowledges that this duty of secrecy creates a clear conflict with NEPA[170]—a conflict moreover that prevents the FDA from fulfilling its NEPA duty to ensure a public airing of significant environmental impacts.

B. ENVIRONMENTAL RISKS POSED BY AQUACULTURE OF TRANSGENIC SALMON

Salmon aquaculture, even of non-transgenic salmon, is already quite controversial, with many scientists claiming that aquaculture endangers the survival of wild salmon.[171]

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167. NAT'L RESEARCH COUNCIL, *supra* note 50, at 111; FUTURE FISH, *supra* note 29, at 52.

168. Indeed, in *Foundation on Economic Trends v. Heckler*, the D.C. Circuit specifically acknowledged the importance of public participation before permitting deliberate release of genetically modified organisms. 756 F.2d 143, 146 (D.C. Cir. 1985).

169. Interview with Eliot Entis, CEO of Aqua Bounty (Oct. 2004) (on file with author).

170. CEQ/OSTP Study, *supra* note 61, at 16.

171. One primary environmental concern with regard to aquaculture is the effect that escaped fish have on wild fish populations. This problem is discussed more fully in section 3, *infra*. Aside from escapees, the process of aquaculture itself raises some serious environmental concerns. For example, aquaculture sea pens freely discharge salmon feces, fish feed and other organic wastes into the aquatic environment. This typically results in excess nitrogen and phosphorous loads in the immediate vicinity of the sea pens. This nutrient overloading causes eutrophication problems. *See* Sena S. De Silva, *Feed Resources, Usage and Sustainability*, *in* SUSTAINABLE AQUACULTURE 221-42 (1999). Underneath every fish pen is a footprint or "dead zone"—a shadow of oxygen depleted and contaminated sediment. United States Pub. Interest Research Group v. Heritage Salmon, Inc. at 4-7, No. 00-150-B-C (D. Me. filed Feb. 19 2002), *available at* http://www.med.uscourts.gov/opinions/kravchuk/2002/MJK_02192002_1-00cv150_ USPISG_v_Heritage.pdf [hereinafter Heritage Salmon]; United States Pub. Interest Research Group v. Atlantic Salmon of Maine at 3-15, No.

Aquaculture of transgenic salmon may pose enhanced or different risks to wild salmon, and it is not at all clear that the FDA has either the scientific competence or the inclination to consider those risks.

1. Transgenic Fish Might Become an Invasive Species

The possible impact of escaped transgenic fish on wild populations is probably the greatest science-based concern raised by the new technology. We already know from experience with conventional aquaculture that physical containment measures fail with disturbing frequency.[172] Conventional farmed salmon are an environmental nuisance

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00-151-B-C, (D. Me. filed May 28, 2003), *available at* http://www.med.uscourts.gov/opinions/carter/2003/GC_05282003_1-00cv151_USPIRG_v_AtlanticSal.pdf [hereinafter USPIRG 2003]. Memorandum of Law in Support of Defendant's Motion to Dismiss or, in the Alternative, for Summary Judgment at 27-29, Int'l Tech. Ctr. v. Thompson, No. 1:04CV00062(RMU) (D.D.C. filed 2004); *see also* T.H. Pearson & K. D. Black, *The Environmental Impacts of Marine Fish Cage Culture*, *in* ENVIRONMENTAL IMPACTS OF AQUACULTURE 1-31 (Kenneth D. Black ed., 2001). Nutrient loading is, of course, a significant and widespread problem attributable to many causes in addition to aquaculture. Nevertheless, nutrient loading from aquaculture can have significant impacts on a local scale. Proper rotation and fallow periods can minimize these effects over the long term. Unfortunately, the industry's track record with rotation and fallow periods is not very good. USPIRG 2003, *supra*, at 14-18.

In addition to organic wastes, fish farms also release a wide range of chemical pollutants including pesticides, antifoulants, and antibiotics. The uncontrolled use of parasiticide drugs like cypermethrin to control sea lice infestations is particularly problematic because cypermethrin is highly toxic to many marine organisms. *Id.* at 4-7. Copper antifoulants are typically used to retard growth of organisms on the sea pen nets. This copper leaches into the marine environment where it can be toxic to wild populations. *Id.* at 6.

172. Alexandra Morton & John Volpe, *A Description of Escaped Farmed Atlantic Salmon* Salmo salar *Captures and Their Characteristics in One Pacific Salmon Fishery Area in British Columbia, Canada, in 2000*, 9 ALASKA FISHERY RES. BULL. 102 (2002). The scope of the problem caused by escaping fish can be staggering. More than 170,000 salmon escaped from a Maine salmon farm during one storm. *See* Atlantic Salmon Fed'n, Catastrophic Salmon Escape Prompts Calls for Moratorium on the Aquaculture Industry (Feb. 22, 2001), *available at* http://www.asf.ca/Communications/2001/feb/catastrophe.html (last visited Apr. 24, 2005). Another 600,000 escaped from a single incident in the Faroe Islands. Jogvan Gardar, *600,000 Faroese Salmon on the Run After Storms*, INTRAFISH, Feb. 28, 2002, *available at* http://www.intrafish.com/article.php?articleID=21073&s= (last visited Mar. 23, 2005). Each year, approximately two million Atlantic salmon escape from aquaculture pens in the North Atlantic. Helen Briggs, *Farm Threat to Wild Salmon*, BBC NEWS, Oct. 20, 2003, *available at* http://www.flmnh.ufl.edu/fish/innews /farmthreat2003.htm (last visited Mar. 23, 2005).

upon escape, competing with wild salmon for food and mating opportunities and encroaching on the ecological niches of other species. Transgenic fish that escape into natural ecosystems could pose a much bigger environmental threat. This danger mainly arises for those transgenic fish endowed with new genes that improve such fitness traits like mating success or the ability to withstand harsh conditions.[173]

Based on what is currently known about transgenic fish, it is impossible to adequately predict the environmental outcomes should these fish escape or be released to the wild. There is little published information about whether or not adult transgenic fish are larger than their conventional counterparts (a variable that tends to relate directly to mating success) but at least one study has shown that transgenic fish modified to produce higher levels of GH not only grow more rapidly, but also grow to a larger size.[174] The establishment of a thriving transgenic fish population in an ecosystem where it has never existed could crowd out native fish populations. These dangers are only poorly understood and have yet to be thoroughly considered by any of the regulatory agencies charged with protecting and preserving the marine environment. There simply is not yet enough information to predict when and where transgenic fish would be likely to become an invasive species.

2. Transgenic Fish Might Bear Trojan Genes

Beyond these more general ecological effects, there are also real concerns about the effects of transgenic fish will have on the genetic diversity of wild populations. A transgenic fish that has a survival advantage in the wild could out-compete its wild relatives. For example, some experimental evidence suggests that transgenic coho salmon modified to express high levels of GH will be able to out-compete wild coho salmon for food.[175] Changes in the genetic make-up of well-adapted wild populations may ultimately affect their abilities to withstand environmental change.

Even if transgenic animals cannot out-compete their wild

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173. Robert H. Devlin et al., *Population Effects of Growth Hormone Transgenic Coho Salmon Depend on Food Availability and Genotype by Environment Interactions*, 101 PROCEEDINGS NAT'L ACAD. SCI. 9303, 9303 (2004).

174. de la Fuente, *supra* note 152, at 89.

175. Devlin, *supra* note 152, at 479.

relatives, transgenic animals might detrimentally affect wild populations by introducing "exotic" genes into wild gene pools. Of particular concern is the so-called "Trojan Gene" effect, whereby transgenic animals that are poorly adapted for survival nonetheless have a mating advantage.[176] For example, many transgenic fish have been modified to generate faster growth and/or larger size, traits typically associated with male mating success.[177] These positive fitness traits are balanced by other characteristics, like reduced swimming speed,[178] and aggressive food pursuit,[179] that suggest the transgenic fish may have a long-term viability disadvantage. This matrix of favorable reproductive traits and maladaptive pleiotrophic traits raise concerns that transgenic fish may introduce Trojan genes to their wild relatives—genes that increase mating success but decrease ultimate viability. Such genes would reduce the mean fitness of the wild populations, and in extreme cases, might drive wild populations to extinction. Possession of Trojan genes might enable transgenic fish to out-compete their conventional counterparts at breeding, thus reducing the overall fitness of the wild population.[180]

At this point, there is evidence that non-transgenic farmed salmon exhibit characteristics which might predispose them to such Trojan gene effects, such as reduced survival of progeny

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176. Muir & Howard, *Possible Ecological Risks*, *supra* note 136, at 13,853. Muir applied this predictive model to GloFish and concluded that any released GloFish could not establish themselves in United States waters as an invasive species. However, he cautioned, "In my opinion, these fish are safe. But again, that's my opinion." *GloFish Risk*, SCIENCENTRAL NEWS, Dec. 23, 2003, *available at* http://www.sciencentral.com/articles/view.php3?article_id=218392134&language=english (last visited Mar. 23, 2005). He also indicated the expectation that the FDA would conduct an independent analysis as to the safety of these fish before permitting their sale in interstate commerce. *Id.*

177. Yoon Kwon Nam et al., *Dramatically Accelerated Growth and Extraordinary Gigantism of Transgenic Mud Loach* Misgurnus mizolepis, 10 TRANSGENIC RES. 353 (2001): R.D. Howard et al., Mate Choice and Mate Competition Influence Male Body Size in Japanese Medaka, 55 ANIMAL BEHAV. 1151 (1998).

178. Anthony P. Farrell et al., *Growth-Enhanced Transgenic Salmon Can Be Inferior Swimmers*, 75 CAN. J. ZOOLOGY 335 (1997).

179. Elisabeth Jönsson et al., *Growth Hormone Increases Predation Exposure of Rainbow Trout*, 263 PROCEEDINGS: BIOLOGICAL SCI. 647 (1996).

180. Muir & Howard, *Possible Ecological Risks*, *supra* note 136, at 13,853; Philip W. Hedrick, Invasion of Transgenes from Salmon or Other Genetically Modified Organisms into Natural Populations, 58 CAN. J. FISHERIES & AQUATIC SCI. 841, 841 (2001).

from farmed and wild salmon matings.[181] When coupled with the growing body of evidence that transgenic fish may possess both the mating advantage and the viability disadvantage central to the Trojan gene scenario,[182] this concern becomes pressing, particularly for the many salmon that are listed as threatened or endangered.

The point is not that aquaculture of transgenic salmon will doom wild salmon to extinction, but that this is a big question mark—an unknown that must be carefully considered before the FDA makes any decision on Aqua Bounty's application. The Trojan gene possibility is largely based on computer simulations of non-salmonid reproduction, and on extrapolations from behavioral studies. Further study is clearly warranted before conclusions can be drawn. The FDA's willingness, based on a complete lack of evidence, to declare that GloFish posed no risks different from its unmodified counterparts, does not lend confidence that the FDA is up to this task.

3. Available Biological Containment Methods Do Not Solve this Problem

In a landmark settlement of a Clean Water Act lawsuit brought by a coalition of public interest organizations, one fish farming company agreed to refrain from growing genetically engineered salmon strains in Maine.[183] The same plaintiffs brought another federal lawsuit against other Maine aquaculture companies and obtained an injunction banning transgenic fish from Maine waters pending further safety

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181. Ian A. Fleming et al., *Lifetime Success and Interactions of Farm Salmon Invading a Native Population*, 267 PROC.: BIOLOGICAL SCI. 1517, 1517 (2000); Philip McGinnity et al., *Fitness Reduction and Potential Extinction of Wild Populations of Atlantic Salmon,* Salmo salar, *as a Result of Interactions with Escaped Farm Salmon*, 270 PROC.: BIOLOGICAL SCI. 2443, 2443 (2003); P. McGinnity et al., *Genetic Impact of Escaped Farmed Atlantic Salmon (*Salmo salar *L.) on Native Populations: Use of DNA Profiling to Assess Freshwater Performance of Wild, Farmed, and Hybrid Progeny in a Natural River Environment*, 54 ICES J. MARINE SCI. 998, 998 (1997)

182. *See generally* Hedrick, *supra* note 180; Richard D. Howard et al., *Transgenic Male Mating Advantage Provides Opportunity for Trojan Gene Effect in a Fish*, 101 PROC. NAT'L ACAD. SCI. 2934 (2004).

183. Nat'l Envtl. Law Ctr., Federal Court Bans Frankenfish & Antibiotics: Judge Approves Landmark Settlement of Clean Water Act Lawsuit Against Heritage Salmon, Inc. (July 29, 2002), *available at* http://www.organicconsumers.org/gefood/frankenfishban (last visited Mar. 23, 2005).

research.[184] In particular, the court ordered that biological containment mechanisms be explored.[185]

Biological containment can reduce the risks to wild fish from escapees. In the context of aquaculture, biological containment typically means raising sterile triploid fish or sterile transgenic fish carrying anti-fertility genes tailored into their genomes.[186] Sterilization techniques are relatively easy and inexpensive, but success rates are highly variable. There is an overwhelming consensus, even among advocates of this technology that neither perfect containment nor 100% sterilization of GM fish will be possible.[187] For example, Yorktown Technology initially claimed that GloFish were triploid and therefore sterile. However, press reports of fertile GloFish reproducing are not uncommon.[188]

Given the huge numbers of fish in commercial aquaculture operations, typically hundreds of thousands per pen, and the concomitant large numbers of escapees, even a small percentage of residually fertile transgenic fish might be enough to pose all the threats of crossbreeding.[189] In addition, even

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184. USPIRG, *supra* note 171, at 42-43.

185. *Id.*

186. P. Alestrom et al., *Fish Gonadotropin-Releasing Hormone Gene and Molecular Approaches for Control of Sexual Maturation: Development of a Transgenic Fish Model*, 1 MOLECULAR MARINE BIOLOGY & BIOTECHNOLOGY 376, 376 (1992); Robert H. Devlin & Edward M. Donaldson, *Containment of Genetically Altered Fish with Emphasis on Salmonids*, *in* TRANSGENIC FISH 229-54 (Choy L. Hew & Garth L. Fletcher eds., 2002); A.R. Kapuscinski & E. M. Hallerman, *American Fisheries Society Position Statement on Transgenic Fishes*, 15 FISHERIES 2 (1990).

187. REX A. DUNHAM, STATUS OF GENETICALLY MODIFIED (TRANSGENIC) FISH: RESEARCH AND APPLICATION 15, *available at* ftp://ftp.fao.org/es/esn/food/GMtopic2.pdf (last visited Apr. 10, 2005); Norman Maclean & Richard James Laight, *Transgenic fish: an Evaluation of Benefits and Risks*, 1 FISH & FISHERIES 146, 166 (2000). Even Aqua Bounty researchers admit that

> [p]resent sterility techniques will probably be adequate for some species in most circumstances, but may not sufficiently reduce risks (or be commercially viable) for other species under other conditions. Considering the lack of present understanding of the fitness . . . of such transgenic fish, it may be exceedingly difficult to predict impacts in many situations.

ARNOLD SUTTERLIN ET AL., ENVIRONMENTAL RISKS IN USING GH TRANSGENIC ATLANTIC SALMON AND RAINBOW TROUT FOR COMMERCIAL MARINE PRODUCTION IN CANADA, *available at* http://www.nbiap.vt.edu/brarg/brasym96/sutterlin96.htm (last visited Mar. 23, 2005).

188. *See, e.g.*, Dawn Fallilk, *supra* note 38, at A1.

189. A.R. Kapuscinski & D.J. Brister, *Genetic Impacts of Aquaculture*, *in*

effective sterilization will not necessarily neutralize the risks to wild populations. Escaped, sterile fish might still engage in courtship and spawning behavior, and therefore disrupt breeding in wild populations and decrease overall reproductive success. Even without reproducing, waves of escaped sterile fish could also create ecological disruptions by competing with wild fish. If transgenic fish have a competitive advantage, wild fish will be overwhelmed as each sterile escapee cohort is replaced by another equally strong cohort. Transgenic fish that do not have a competitive advantage would still stress fragile marine ecosystems through their sheer numbers. Again, the FDA's GloFish decision does not generate confidence that the FDA will fully consider these concerns.

4. Transgenic Salmon Might Have an Enhanced Ability to Transfer Disease

Genetic engineering has also focused on increasing resistance of fish to pathogens.[190] The possibility of increased resistance is of obvious commercial interest. However, it does raise an additional environmental concern. Transgenic fish might act as reservoirs for diseases and parasites to which they are resistant—thereby increasing the risk of transferring diseases and/or parasites to wild populations.[191]

Aquaculture already creates disease reservoirs.[192] For

ENVIRONMENTAL IMPACTS OF AQUACULTURE 128-53 (2001).

190. *See generally* Garth S. Traxler et al., *Naked DNA Vaccination of Atlantic Salmon,* Salar salar *Against IHNV,* 38 DISEASES AQUATIC ORGANISMS 183 (1999); Niels Lorenzen et al., *Immunity to VHS Virus in Rainbow Trout,* 172 AQUACULTURE 41 (1999); Philippa Melamed et al., *The Potential Impact of Modern Biotechnology on Fish Aquaculture,* 204 AQUACULTURE 255 (2002).

191. *See, e.g.,* O. Tully et al., *Spatial and Temporal Variation in the Infestation of Sea Trout (*Salmo trutta *L.) by Caligid Copepod* Lepeophtheirus salmonis *(Krøyer) in Relation to Sources of Infection in Ireland,* 119 PARASITOLOGY 41 (1999).

192. Aquaculture crowds carnivorous fish into densities not found in the wild. A typical sea pen can contain anywhere from 5000 to 16,000 fish, and a single farm can stock as many as 250,000 fish. USPIRG 2003, *supra* note 171, at 6. This crowding facilitates the spread of disease among the farmed fish. Because the sea pens are open to the environment, pathogens can be dispersed by tidal currents or from feces and urine of infected salmon. The population density within a sea pen allows the amplification of pathogen and parasite loads for subsequent transmission back to wild populations. *See* Richard L. Saunders, *Potential Interaction Between Cultured and Wild Atlantic Salmon,* 98 AQUACULTURE 51, 52-55 (1991). Farmed fish thus serve as a reservoir for diseases that can be spread to wild fish. *See generally* C.D. Todd et al., *Genetic*

example, sea lice infestations are endemic in most areas with intensive salmon culture.[193] Salmon farms have been correlated with a more than three-fold increase in abundance of lice infestations of wild fish.[194] When salmon farms are situated along salmon migration routes, or in wild salmon habitats, the results can be devastating to already-endangered wild populations. For example, major sea lice infestations in British Columbia have been correlated with significant decreases in numbers of fish returning to spawn,[195] and are believed to be responsible for the catastrophic collapse of the wild sea trout population.[196] Bacterial and viral diseases like infectious salmon anemia also run rampant in fish farms and can infect wild populations.[197]

In conventional aquaculture, the disease reservoir risk posed by aquaculture is necessarily limited by the possibility that the disease will kill its host fish. Creating transgenic fish immune to the disease would increase the risk dramatically because infected fish could serve as hosts for the infectious agent without expressing any of the negative manifestations of the disease. Infected transgenic fish could persist for long periods of time, thus spreading the infection or disease.

CONCLUSION: WHERE TO GO FROM HERE?

The status quo resembles a vacuum more than it does a coherent and functional regulatory scheme. States have been stepping in to fill that vacuum, and, have imposed a growing

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Differentiation of Populations of the Copepod Sea Louse Lepeophtheirus salmonis *(Krøyer) Ectoparasitic on Wild and Farmed Salmonids Around the Coasts of Scotland: Evidence from RAPD Markers*, 210 J. EXPERIMENTAL MARINE BIOLOGY & ECOLOGY 251 (1997); Tully, *supra* note 191.

193. WATERSHED WATCH SALMON SOC'Y, SALMON FARMS, SEA LICE AND WILD SALMON (2001), at 10, *available at* http://www.watershed-watch.org/ww/publications/SeaLice/SeaLicePaper.html (last visited Mar. 23, 2005); *see also* David Suzuki Found., Diseases Associated with Salmon Farms, *available at* http://www.davidsuzuki.org/Oceans/Fish_Farming/Salmon/Diseases.asp (last visited Mar. 23, 2005).

194. *See* WATERSHED WATCH SALMON SOC'Y, *supra* note 193, at 8-9, 11; Tully, *supra* note 192, at 49.

195. Rosamond L. Naylor et al., *Salmon Aquaculture in the Pacific Northwest: A Global Industry*, ENV'T, Oct. 2003, at 18, 27, 29-30.

196. Pearson & Black, *supra* note 171, at 20.

197. NAT'L RESEARCH COUNCIL, ATLANTIC SALMON IN MAINE 82, 151-52, (2004), *available at* http://www.nap.edu/books/0309091357/html (last visited Apr. 10, 2005).

array of restrictions on transgenic fish.[198] State regulation is an imperfect response to this problem. Indeed many of those commenting on California's GloFish ban point out how easily residents can acquire the fish from neighboring states.[199] Piecemeal state regulation also raises the specter of inconsistent obligations that might make marketing the products of biotechnology nearly impossible. National standards are necessary.

To forestall inconsistent state regulation, to promote confidence in the technology, and most importantly, to protect human health and the environment, we must develop a sound, transparent, and credible method for evaluating the environmental risks associated with transgenic fish. A consistent program of risk assessment is necessary. Scientists have already developed the beginnings of a reasonable model for such a risk assessment.[200] This system is far from perfect but could be the starting point for a scientifically sound agency risk evaluation of genetically modified fish. In order for that to occur, the FDA must live up to its statutory role and must resolve any conflicts between its statutory mandates and the Coordinated Framework in favor of fully implementing its statutory mandates.

The Coordinated Framework must also be reconsidered, either by the President and the Executive Branch itself or through legislative action. In particular, it is time to rethink

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198. In addition to the California regulatory scheme described earlier, the following additional state level measures are in place. After *USPIRG v. Heritage Salmon Inc.*, transgenic salmon are banned in Maine. Oregon and Washington ban these fish by statute. OR. ADMIN. R. 635-007-0595 (2004); WASH ADMIN. CODE § 220-76-100 (2004). Maryland prohibits introduction of transgenic fish into waters of the State that flow into any other body of water. MD. CODE ANN. § 4-11A-02 (2000). Michigan recently passed a law imposing criminal penalties for violation of the prohibition against the release of genetically engineered fish. Michigan Aquaculture Development Act, 2004 Pub. Acts Nos. 270, 272. Minnesota and Mississippi have adopted rules for the issuance of permits for release of genetically engineered organisms. MINN. STAT. § 18F.01-.13 (2004); MISS. CODE ANN. § 79-22-9 (2000). Wisconsin has a notification and review process before release of genetically modified organisms into the environment. WIS. STAT. ANN. § 146.60 (2000).

199. *See, e.g.*, Associated Press, *California Blocks Sale of GloFish Pets*, Dec. 4, 2003, *available at* http://www.flmnh.ufl.edu/fish/innews/glofish2003.htm (last visited Apr. 22, 2005); Posting of Chris Mooney, California Bans Glofish, to www.chriscmooney.com (Dec. 4, 2003), *at* http://www.chriscmooney.com/blog.asp?Id=478 (last visited Apr. 22, 2005).

200. *See generally* William M. Muir, *The Threats and Benefits of GM Fish*, 7 EUR. MOLECULAR BIOLOGY ORG. REP. 654 (2004).

the decision to make the FDA lead agency for regulating transgenic fish (and other animals). Because many of the most critical issues with regard to transgenic fish are environmental, they do not naturally fall within the FDA's scope of authority.

The situation cries out for congressional clarification of how transgenic animals should be regulated. Ideally Congress would decide to channel regulatory decisions to the EPA and Fish and Wildlife Service—agencies with some expertise in assessing environmental safety and risks. However, the FDA must not wait for Congress or the President before undertaking its own rethinking of how it approaches transgenic animals. For starters, the FDA should ensure that it fully exercises its statutory mandates under FDCA and NEPA. Through proper interpretation of its statutory mandates, the FDA can ensure that every transgenic animal is subject to a rigorous new animal drug scrutiny, and can make environmental effects of these transgenic animals a central consideration in the regulatory analysis. The FDA should make it clear that, at least at the beginning when there are so many unknowns, every transgenic animal will be subject to stringent environmental and human health assessments. The many unanswered environmental questions posed in this article and elsewhere can provide a starting point for the FDA's thorough and public consideration of any NAD applications it may receive. Only then will the environmental risks posed by this technology be addressed and public mistrust assuaged.