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# What Would You Do with a Fluorescent Green Pig?: How Novel Transgenic Products Reveal Flaws in the Foundational Assumptions for the Regulation of Biotechnology

Part 2

by

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The policy decisions made in the Coordinated Framework were inspired, at least in part, by the goal of limiting regulatory restrictions that might hamper the development of the promising and fledgling biotechnology industry.[216] However, because the field of genetic engineering is relatively new and has advanced so quickly in recent years, there is tremendous uncertainty regarding the existence and degree of risk presented by GMOs and their progeny.[217] Requiring a challenger to demonstrate harm in order to trigger extraordinary scrutiny of a GM product significantly reduces the manner and extent to which federal regulators are able to address novel products of biotechnology intended for food use. By maintaining a very broad definition of "substantial equivalence," federal agencies have committed to a reactive approach to regulating unforeseen complications, waiting for problems to manifest before applying heightened scrutiny to, or attempting to withdraw, a GM product.

### *B. Criticism of the Coordinated Framework*

Over the past two decades, many criticisms have been levied regarding the content, omissions, and implementation of the Coordinated Framework. Experience has shown that the expectations of the framework have not borne out, nor has the framework provided the organized, predictable, and comprehensive regulatory process that the originators intended.

From inception, the Coordinated Framework identified two primary objectives for the various agencies regulating GM products: that the agencies "adopt consistent definitions" of GMOs, and that the agencies implement scientific reviews of "comparable rigor" in their regulation of GM products.[218] Neither of these objectives has been met,[219] largely due to inflexibility stemming from the assumptions underlying the Coordinated Framework, with the result that bioengineered products are "regulated under laws enacted long before such products were considered possible."[220] Agencies must manipulate existing definitions and authority to fit transgenic products into a regulatory structure that was not specifically designed to handle them.[221]

The Coordinated Framework presumes that the required level of review for a GMO is based on the degree of risk presented by each use of

216. *See* Mandel, *supra* note 187, at 2216.

217. *See generally* Applegate, *supra* note 185, at 207.

218. Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302, 23,303 (June 26, 1986).

219. *See* Mandel, *supra* note 187, at 2236–37.

220. *Id.* at 2242–43.

221. *See id.* at 2243.

the organism. Under the Coordinated Framework, the assessment of risk is an evolving process.

> The regulatory framework anticipates that future scientific developments will lead to further refinements. Experience with earlier basic scientific research has shown that as the science progressed and became better understood by the public, regulatory regimens could be modified to reflect more complete understanding of the potential risks involved. Similar evolution is anticipated in the regulation of commercial products as scientists and regulators learn to predict more precisely particular product use[s] that require greater or lesser controls or even exemption from any federal review.[222]

The FDA follows this use-based risk assessment—determining that food usage is different from drug usage and that each product used requires its own level of precaution and pre-market analysis. The minimal scrutiny applied to GM crops can be seen as an early step toward the complete exemption from federal review of GM products incorporating a new protein considered to be entirely safe. Ultimately, any GM crop that merely incorporates a previously scrutinized new protein will be marketable with no regulatory review at all.

Despite its regulation-limiting foundation, the Coordinated Framework notes that the filing of "new marketing applications will be required for most products manufactured using new biotechnology."[223] The requirement for such new or supplemental product approval applications demonstrates the conflict between the goals and the methods of the Coordinated Framework. Although the Coordinated Framework is intended to improve efficiency in the review and approval of GM products, it creates additional review requirements for the products covered. In practice, the FDA has not required a new marketing application for any of the GM food products introduced into the U.S. marketplace.[224]

In addition to internal conflicts, the Coordinated Framework also leaves gaps in regulatory authority that agencies are forced to work around using existing authority. For example, the Coordinated Framework does not address the regulation of transgenic pest-protected

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222. Coordinated Framework, 51 Fed. Reg. at 23,303.

223. Statement of Policy for Regulating Biotechnology Products, 51 Fed. Reg. 23,302 (June 23, 1986). The new marketing application is either an entirely new application for product approval, such as a New Drug Approval or New Animal Drug Approval application for the GM product, or a supplemental application for GM products that are identical or virtually identical to conventional products, based on an individual product consideration by the FDA.

224. *See* Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. 22,984, 22,986 (May 19, 1992); *see also* Alliance for Bio-Integrity v. Shalala, 116 F. Supp. 2d 166 (D.D.C. 2000) (dismissing challenge to the FDA's decision not to regulate genetically modified food differently from conventional food).

plants.[225] Nonetheless, these products were field tested and commercialized shortly after the Coordinated Framework was promulgated and are now among the most widely used GM products.[226] The Coordinated Framework does not specify a lead agency for evaluation of GM fish and other bioengineered aquatic organisms, although the Coordinated Framework's originating documents required this task.[227] The largest gaps in regulatory authority under the Coordinated Framework relate to products that are not intended for food or drug uses, and for risks that do not directly impact human or livestock health. The introduction and analysis of current transgenic products in Part V illustrates these lapses in regulatory authority.[228]

The Coordinated Framework assumes that GM products should not be regulated based on the process that creates them, but rather on just the new proteins within the product.[229] Further, the Coordinated Framework presumes that no new statutory authority is necessary to regulate GM products. [230] These assumptions influence regulators to minimize their conception of the risks posed by GM products.[231] Under the Coordinated Framework, only the new protein poses a risk, and over time all of the new proteins will have received scrutiny. However, in the years since its inception, the agencies responsible for implementing the Coordinated Framework have modified their original positions regarding both the degree of risk involved in bioengineering and the adequacy of focusing regulation on products rather than processes.[232] The FDA, APHIS, EPA, and the National Research Council have all since determined that certain GM products should be regulated based on the process by which they were created, not just by *comparison* with non–genetically engineered products.[233] These policy determinations reveal resistance to the foundational assumptions of the Coordinated Framework.[234]

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225. *See* NAT'L RESEARCH COUNCIL, *supra* note 69, at 26.

226. *See* Mandel, *supra* note 187, at 2245.

227. *See* PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, FUTURE FISH: ISSUES IN SCIENCE AND REGULATION OF TRANSGENIC FISH 37 (2003), *available at* http://pewagbiotech.org/research/fish (noting that the Coordinated Framework failed to "specify the lead agency for transgenic fish and other [transgenic] aquatic organisms").

228. See *infra* discussion accompanying note 251.

229. *See* text accompanying *supra* note 191 (discussing the product versus process regulatory distinction under the Coordinated Framework).

230. *See* Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302, 23,303, 23,309, 23,336 (June 26, 1986) (asserting that the new regulations are not needed to address genetically modified products).

231. *See id.*

232. *See* Mandel, *supra* note 187, at 2244–45.

233. *See id.*

234. *See id.* at 2245.

The Coordinated Framework burdens the FDA to assert regulatory authority under the FDCA over a tremendous variety of products. However, the FDA Center assigned to assess a GM product may not be an efficient or effective regulator due to a lack of the necessary institutional experience, knowledge, or capacity to effectively identify and oversee each of the risk implications of that product. In addition, the absence of explicit legal authority to regulate the variety of risks implicated by the product further constrains regulatory ability.[235]

The fit of bioengineering regulation under the FDCA is as problematic for drugs as it is for foods. Innovative medical use products are not easily categorized into the three existing categories of drug, device, or biologic utilized by the FDA,[236] leading to confusing and arbitrary category assignment. The newest technologies often involve a combination of two or more of these components. Since the regulatory requirements and level of oversight differs for each drug category under the FDCA, inconsistent assignment can have drastic impact on the level of review and risk avoidance applied by the regulator. The FDA created the Office of Combination Products to address this problem for nontransgenic products, but has no such structure for GM products. Although the FDA publishes guidance documents to make specific recommendations to the industry, and consults both within the agency and external entities on difficult issues, the biotechnology industry continues to be burdened by complex, uncertain, and repeatedly changing regulatory schemes.[237] This experience directly conflicts with the efficiency and economy purposes for which the Coordinated Framework was established.

The failure of the current regulatory structure, under the Coordinated Framework, to effectively handle existing biotechnology products raises the concern that the existing system will prove to be even more problematic as new and more complex risks and issues are introduced.[238]

### *C. Response to the Coordinated Framework*

Since 1992, the FDA has published a number of draft guidance documents to lead the biotechnology industry through the regulatory

235. *See id.* at 2243.

236. *See* Martha J. Carter, *The Ability of Current Biologics Law to Accommodate Emerging Technologies*, 51 FOOD & DRUG L.J. 375, 376 (1996). For example, recombinant proteins have been classified both as drugs and as biologics. In addition, fields such as genomics and proteomics may technically fit into the biologic category, yet introduce complexity that was never imagined when the category of biologic was first conceived.

237. *See* Mandel, *supra* note 187, at 2231, 2249, 2251.

238. *See id.* at 2246.

process in the absence of specific regulations.[239] This guidance, some of which was eventually officially promulgated, finds its authority in general statutes written long before the biotechnology industry emerged. Throughout these documents, the FDA repeatedly claims that "[b]ioengineered foods do not pose any risks for consumers that are different from conventional foods."[240] The FDA claims that its review processes will ensure that there are no hazards, such as unexpected allergens or poisonous substances, in foods and that nutritional value is not reduced.[241] To accomplish this goal, the FDA explains that its efforts to ensure the safety of bioengineered foods include publishing rigorous safety testing guidelines, establishing a consultation process with industry, and seeking expertise outside of the agency.[242] However, this oversight plan remains largely voluntary, especially in the case of GM crops, requiring the public to depend upon industry willingness to follow nonbinding guidance.

Despite repeated assurances that the regulatory oversight of bioengineered products is adequate to identify and address potential hazards, the U.S. government has been broadly criticized by both state and local governments,[243] as well as by foreign governments and nongovernment organizations,[244] for its perceived lax regulation of genetically modified products. However, some international biotechnology guidelines for food products have been established that track those of the United States. For example, in July 2003, the Codex Alimentarius Commission adopted international guidelines for GM food safety consistent with the FDA approach.[245] Nonetheless, consideration of

239. *See infra* note 438 and surrounding discussion.

240. See Bren, *supra* note 97 (quoting James Maryanski, Food Biotechnology Coordinator, FDA).

241. *See id.*

242. *See id.*

243. *See* Daisy Nguyen, *Bans on Genetically Engineered Crops in California Counties Spark Push for State Control*, MAIL TRIBUNE (Oregon), July 13, 2005, *available at* http://www.mailtribune.com/archive/2005/0713/biz/stories/01biz.htm. For example, voters in three California counties: Mendocino, Marin, and Trinity, passed laws banning the use of genetically altered seeds. Voters in several other states and California counties rejected such initiatives. In response to the bans, as of late 2004, fourteen states had passed bills that bar towns, cities and counties from regulating genetically engineered crops, and a nationwide effort to establish such bans in every state is ongoing.

244. *See, e.g.*, Applegate, *supra* note 185, at 207; (considering the implications of the U.S. approach to GM risk assessment on industry and consumers); Marden, *supra* note 211, at 786–87 (exploring the divergence of U.S. and international attitudes regarding GM food product safety); Stephen Leahy, *Ban Endures on Terminator Seeds*, Inter Press Service News Agency, Feb. 11, 2005, *available at* http://www.ipsnews.net/interna.asp?idnews=27410 (discussing international criticism of terminator seed technology).

245. *See* Bren, *supra* note 97. Codex, an entity established by the World Health Organization and the Food and Agriculture Organization of the United Nations, is the premier international body on food standards. *See id.*

GM foods in Europe, Asia, Africa, and South America has been fraught with controversy and many countries have prohibited the import of bioengineered products, the growth of crops from GM seeds, and even the donation of GM foods for humanitarian purposes.[246]

Within the United States, consumer acceptance of GM products is limited. In 2006, the Pew Initiative on Food and Biotechnology released the poll results revealing that public awareness and understanding of GM foods remains relatively low and has declined in recent years.[247] Although U.S. farming largely accepts GM technology,[248] consumers' opinions about GM foods remain divided and only 34 percent of those polled responded that they felt GM foods were basically safe.[249] In general, Americans support federal regulation of GM foods, with 41 percent feeling that there is too little regulation in this area.[250]

Creation of enforceable law through the promulgation of new FDA regulations or additional legislation, rather than reliance on nonbinding guidance documents and voluntary review processes, would provide a more dependable and certain regulatory matrix upon which both industry and the public can depend. Consistent and rigorous oversight of the bioengineering field might allay some of the fears regarding GM crops, and promote a more accepting attitude toward transgenic goods among state, local, and international entities.

## V. REGULATORY CHALLENGES OF MODERN TECHNOLOGY

As genetic engineering blurs the lines between plants, animals, and industrial products, cross-kingdom transgenic organisms present a particular challenge. The regulator must determine under which regulatory scheme a novel organism should be examined, despite the fact that the organism expresses genetic traits from completely unrelated sources. For example, classification of a crop plant that expresses industrial use chemicals following the introduction of an animal gene into the plant's DNA is not a simple task. The potential risks posed by the plant are not just those of the plant progenitor, nor those of the animal

246. *See* sources cited *supra* note 244.

247. *See* Review of Public Opinion Research, Memorandum from The Mellman Group to Pew Initiative on Food and Biotechnology (Nov. 16, 2006), *available at* http://pewagbiotech.org/research/2006update/2006summary.pdf. The survey was conducted by telephone by the Mellman Group and Public Opinion Strategies, September 20–26, 2006, and included one thousand American consumers.

248. *See id.* at 1. For example, the percentage of GM corn planted rose from 26 percent to 61 percent during the time period covered by the survey.

249. *See id.* at 3–4 (showing 29 percent of those polled believed GM foods to be basically unsafe, and 37 percent did not have an opinion).

250. *See id.* at 5 (41 percent of consumers who claim basic awareness of GM regulation said there is too little regulation, 19 percent said the amount was right, and 16 percent said there is too much regulation).

progenitor. Because the Coordinated Framework and the FDA take an intended-use, individual product–based approach to regulation, if the GMO developer claims that a new organism is intended for a certain use, such as for animal feed, it will most likely be scrutinized under the corresponding animal feed regulatory matrix.[251] However, trouble arises if the proponent claims that the organism is to be used for neither food nor drug purposes, such as was the case with the first transgenic animal offered for sale to the public, the GloFish.[252] GM products intended for industrial use, or for any use outside of the FDCA's food and drug definitions, may be allowed to enter the market without a review of the special hazards to the environment posed by the organism or its progeny, and perhaps without any FDA review at all.

After describing novel trangenic organisms and their regulation, this Part reviews the special challenges posed by three such organisms currently entering the marketplace: the pet GloFish, the medical research subject GFP Pig, and the consumable transgenic salmon. This is followed by a discussion of biopharming, the process of producing pharmaceutical products via genetic engineering of crop plants. GM plants pose somewhat different challenges to the regulator than GM animals, but this Comment shows that many of the hazards to the environment, and the challenges in applying the Coordinated Framework, are shared with the GM animals.

### *A. Novel Transgenics*

#### *1. Defining Novel Wide-Cross Organisms*

Advances in biotechnology over recent years have facilitated a tremendous increase in the number and types of genetic modifications attempted by bioengineers, resulting in the combination of genes from very different genera, phyla, and even kingdoms. Human genes, for example, can be implanted in a corn variety, in the hopes of quickly producing a human protein for medical use.[253] Any type of hybridization that cannot be generated through cross-fertilization is categorized as a "wide cross" by the FDA. According to the FDA, these wide crosses are "useful for expanding the range of genetic source material that can be introduced into food crops."[254] As recently as 2001, however, the FDA claimed that such wide crosses would be "performed relatively

251. *See supra* note 176 and surrounding discussion.

252. *See* Part V.B.1 for further discussion of the GloFish experience with the FDA.

253. *See* Rowena C. Seto, *Selling the Pharm: The Risks, Benefits, and Regulation of Biopharmaceuticals*, 27 ENVIRONS ENVTL. L. & POL'Y J. 443, 453 (2004).

254. FDA Premarket Notice Concerning Bioengineered Foods, 66 Fed. Reg. 4706, 4710 (proposed Jan. 18, 2001) (to be codified at 21 C.F.R. pts.192 & 592).

infrequently because of technical and logistical difficulties."[255] Recent experience shows that this view is out of date with the current practice of the biotechnology industry.

Under the specific comparison approach of the FDCA and the Coordinated Framework, the current trigger for increased scrutiny of a GMO is the demonstration of an element in the new organism that is physically different from the progenitor organisms.[256] The scrutiny extends only to the elements in the recipient organism that are shown to be different from conventional analogs. Unfortunately, as innovation increases in GM application, it becomes difficult to determine the conventional organism to which the transgenic elements should be compared. This suggests the need for a new regulatory test to determine when elevated scrutiny is appropriate for a novel organism. A distinction could be drawn based on the taxonomic distance between the donor organisms, the effort or technology required to achieve gene combination, or even on the lack of consumer or producer familiarity with the final transgenic product. The last could be framed as a sort of "ick test"—does the new organism intuitively seem so different that it makes consumers uneasy?[257]

Despite the presumption of safety underlying the Coordinated Framework, the products of wide-cross bioengineering logically and intuitively may require regulatory scrutiny beyond that of more closely related hybrids. Such caution is warranted by the uncertainty in how the newly combined proteins will affect the host organism and its environment. Some transgenic organisms are so innovative and based on such wide crosses that they pose clear questions of safety either in themselves or in their impact on the delicate ecological balance.[258] The innovative wide cross results in a final organism that is distinct from its donor organisms, and as a whole is unprecedented in nature. These novel transgenics cannot reasonably be assumed, as a class, to pose no threat upon entry into the environment—to dependant organisms, to competitors for resources, or to predators, as simple examples. In addition, a focus just on the proteins combined in the novel transgenic, as required under the Coordinated Framework, might not identify the broader impacts of the gene-mixing on the resulting organism itself.

Determining the appropriate level of scrutiny for a wide-cross GMO is largely a matter of judgment. Because a goal of the Coordinated

255. *Id.*

256. *See supra* note 187 and surrounding discussion.

257. Gilhooley, *supra* note 16, at 1109–10 (arguing that the lack of consumer familiarity with a transgenic agricultural product should be enough to trigger increased scrutiny, or at least disclosure through product labeling, and that products achievable without biotechnology need not be labeled even if derived from biotech methods).

258. *See* case studies in Part V.B.

Framework is to promote the bioengineering field, keeping regulatory requirements to a minimum while still addressing the safety needs of the public is vital.[259] One potential method for determining which GMOs should be subjected to heightened scrutiny, or perhaps any scrutiny, would be to establish a line based on how distantly related the donors must be before the resulting GMO requires advanced regulatory scrutiny. For example, any GMO considered a new species would be subject to heightened scrutiny.

There are several ways to determine when a new species has been created. The scientific method for determining what constitutes a species relates to the capacity for interbreeding. Because many wide crosses are not capable of interbreeding with their progenitor organisms, they would be designated a new species.[260] As an alternative, the FDA characterizes as the "same species" only those novel organisms in which the combination of all donor organisms is possible through narrow crosses or hybridization.[261] The FDA recognizes that wide crosses cannot be generated through cross-fertilization. However, the Environmental Protection Agency maintains a broader conception of a single species, regarding wide crosses as part of the definition of conventional plant breeding for purposes of regulating plant pesticides.[262] For efficient and consistent regulatory oversight, such definitional discrepancies between agencies should be eliminated. The species line is definite enough for the agencies to be able to administer, and narrow enough that genetic manipulation of related species will not be subjected to enhanced regulatory requirements.[263]

However, not all wide crosses may be different enough from the parent organisms to trigger elevated scrutiny under any of these tests. Some wide crosses have been derived without the intervention of genetic engineers. A number of currently marketed agricultural food products are the result of wide crosses made through extended methods of plant breeding and tissue culture techniques, allowing wide crosses that

259. *See supra* note 216 and surrounding discussion.

260. *See* Gilhooley, *supra* note 16, at 1108; D. PETER SNUSTAD ET AL., PRINCIPLES OF GENETICS 745–46 (1997).

261. *See* FDA Premarket Notice Concerning Bioengineered Foods, 66 Fed. Reg. 4706, 4710 (proposed Jan. 18, 2001) (to be codified at 21 C.F.R. pts. 192 & 592). The FDA's focus in this notice was on conventional breeding versus genetic engineering, not on the distinction between narrow and wide crosses.

262. *See* 40 C.F.R. § 174.3 (2006); Regulations Under the Federal Insecticide, Fungicide, and Rodenticide Act for Plant-Incorporated Protectants (Formerly Plant-Pesticides), 66 Fed. Reg. 37,772, 37,795 (July 19, 2001); *see also supra* note 261.

263. The burden on the regulatory structure may not be too great, considering that as recently as 2001, the FDA explained that "the most commonly used breeding method is a 'narrow cross', which is hybridization between varieties of the same species." FDA Premarket Notice Concerning Bioengineered Foods, 66 Fed. Reg. at 4710; *see also* Gilhooley, *supra* note 16, at 1108.

produce genetic combinations that could not occur in nature.[264] The products of these techniques have been in use for dozens of years, and include now common varieties of rice, corn, oats, potato, tomato, and sugar beet.[265]

Certainly, more experience and analysis is required to determine which, if any, of the options for triggering heightened scrutiny is best to identify and address an increase in risk to health and safety posed by a novel GMO. However, the Coordinated Framework's presumption of safety may preclude such considerations.

### *2. FDA Authority to Consider Environmental Risks of Transgenics*

The FDA's authority over nonconsumptive uses of transgenic plants and animals is limited by the express purpose of the FDCA to protect the American public from ingesting unsafe or ineffective foods and drugs.[266] This focus does not provide authority over the risks to human safety and the environment posed by nonfood or nondrug uses of a transgenic product, such as industrial or nonconsumptive uses of plants and animals. The FDA has limited resources, and perhaps limited incentive, to conduct a broad exploration of the environmental concerns raised by the genetic engineering of products not directly consumed by humans, or to the plants and animals people consume. However, were the FDA to interpret its authority under the FDCA broadly enough to cover the impact of a transgenic organism on the food chain itself, the FDA arguably would have authority over all GMOs with regard to their impact on other living organisms. Thus, ecological impacts would be subject to FDA oversight without alteration of current statutes.

Proof that the FDA considers ecological and environmental impacts of transgenic products is tenuous. The Office of Science and Technology Policy 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."[267] The FDA did consider potential environmental harms in the new animal drug approval process in the early 1990s for the growth hormone known as "recombinant bovine

264. *See* J. Howard Beales III, *Modification and Consumer Information: Modern Biotechnology and the Regulation of Information*, 55 FOOD & DRUG L.J. 105, 106 (2000); *see also* Food Labeling; Foods Derived from New Plant Varieties, 58 Fed. Reg. 25,837, 25,840 (Apr. 28, 1993) (recognizing that most commercially produced tomatoes contain genetic traits derived from crosses with related weedy species).

265. *See* Gilhooley, *supra* note 16, at 1109–10.

266. *See* Federal Food, Drug, and Cosmetic Act of 1938 §§ 402, 501, 512, 21 U.S.C. §§ 342, 351, 360b(a) (2006).

267. OSTP, GROWTH-ENHANCED SALMON, *supra* note 150, at 14; *see also* 21 C.F.R. § 25.15(b) (2006) (directing FDA to consider whether a proposed action might significantly affect the human environment).

somatotrophin" (rBST), which is produced by genetically engineered bacteria.[268] The FDA considered the environmental risks that the new animal drug might pose, including: (1) changes in land-use patterns and water quality due to impact on the types of feed ingredients grown for dairy cows; (2) carbon dioxide emissions due to changed cattle ration requirements and dairy populations; and (3) syringe disposal problems.[269] The FDA's authority to consider these environmental impacts was not challenged in the approval process for rBST and the FDA approved rBST as a new animal drug in 1993.[270] However, the environmental issues considered in the rBST approval process closely related to direct human health concerns, not just to environmental harms. The FDA's ability, or desire, to consider risk or damage to ecosystems or wild species remains uncertain.

Advocates of the position that the FDA does perform environmental analysis of GM products cite a 1998 FDA guidance document that addresses the environmental impacts of biologics (biologically-based medical products such as blood products and vaccines) under FDCA authority as evidence that the FDA's new animal drug approval requires consideration of a wide range of environmental harms.[271] For biologics, the FDA considers potential harms with "lasting effects on ecological community dynamics," or that "significantly affect the quality of the human environment."[272] Unfortunately for the regulation of transgenics, GMOs are not biologics and the guidance document is limited to circumstances in which "available data establish that there is a potential for serious harm to the environment at the expected level of exposure."[273]

Even if the 1998 biologics guidance applied to new animal drugs, the lack of data regarding the impact of escaped and captive GMOs on the environment would prevent the triggering of such an environmental review under the FDCA. A reasonable goal in the regulation of GMOs would be to identify and address the hazards posed by the organism before it is released into the environment, rather than to attempt to recall

268. *See* PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, *supra* note 227, at 48 n.6.

269. *See id*; *see also* Stauber v. Shalala, 895 F. Supp. 1178, 1186 (W.D. Wisc. 1995) (considering the FDA express consideration of environmental risks that rBST might pose, including changing land use patterns); OSTP, GROWTH-ENHANCED SALMON, *supra* note 150, at 1, 15.

270. 16 FDA DRUG AND DEVICE PRODUCT APPROVALS 355 (1993), *available at* http://www.fda.gov/cder/da/ddpa93.pdf (listing approval for Posilac, NADA number 140-872, Monsanto's Recombinant DNA derived methionyl bovine somatotropin, as of Nov. 5, 1993).

271. *See* CTR. FOR DRUG EVALUATION & RESEARCH, FDA, GUIDANCE FOR INDUSTRY: ENVIRONMENTAL ASSESSMENT OF HUMAN DRUG AND BIOLOGICS APPLICATIONS 6 (1998), *available at* http://www.fda.gov/cder/guidance/1730fnl.pdf.

272. *Id.*

273. *Id.*; *see also* Bratspies, *supra* note 152, at 474.

the organism and its progeny, and remedy the harm after release.[274] The 1998 biologics guidance does not suggest that the FDA will require applicants to either investigate or develop data regarding the likely ecological consequences of their proposed GM products.[275] The government concedes that the FDA's authority may not extend to all environmental impacts, particularly those environmental impacts not directly felt by human beings or animals.[276]

The first transgenic animal expected to be commercially manufactured for human and livestock consumption is a fish.[277] The primary concerns currently raised by transgenic fish involve environmental risks, regardless of whether the fish are meant for human or livestock consumption.[278] The fact that the FDA allowed the commercial release of the first transgenic animal, the pet GloFish, without substantial review of the hazards the creature presented to the environment suggests that the FDA does not perceive the 1998 biologics guidance to require environmental review for GMOs. The FDA's decision not to regulate the GloFish does nothing to inspire public confidence that the FDA will act on the concerns of environmental protection. The limits inherent to the FDA's regulatory mandate and authority under the FDCA raise real questions about whether the FDA, under the Coordinated Framework, has the desire, flexibility, and expertise to address the environmental and ecological issues unique to transgenic organisms.

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274. The FDA potentially could rely on the National Environmental Policy Act (NEPA) as authority to regulate the environmental impacts of genetically modified fish and other animals. The approval of a new animal drug application constitutes a federal action under NEPA. However, such regulation would likely be performed by the EPA, not the FDA, undermining the value of the FDA assertion of authority. *See* 42 U.S.C. § 4332 (2006) (addressing ability of agencies to work in concert, such as an FDA and EPA cooperative effort). The FDA would also face difficulties in complying with NEPA's public participation requirements, since both the FDCA and the Trade Secret Act, prohibit the agency from revealing any trade secret information acquired as part of the new animal drug approval process. *See* Trade Secret Act, 18 U.S.C. § 1905 (2006); Federal Food, Drug, and Cosmetic Act of 1938 § 301(j), 21 U.S.C. § 331(j) (2006). These topics fall outside of this discussion of the application of the FDCA.

275. *See* Bratspies, *supra* note 152, at 474.

276. *See* OSTP, GROWTH-ENHANCED SALMON, *supra* note 150, at 1, 14.

277. *See infra* note 318 and surrounding text (discussing transgenic salmon in detail).

278. *See* PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, *supra* note 227, at 11–26; *see also* NAT'L RESEARCH COUNCIL, ANIMAL BIOTECHNOLOGY: SCIENCE-BASED CONCERNS 9, 73 (2002), *available at* http://books.nap.edu/books/0309084393/html.

## B. Examples of Current Transgenics Challenging the Framework and the FDCA

### 1. GloFish

The first commercially saleable genetically modified animal, the GloFish, entered the market in the United States on January 5, 2004.[279] The GloFish is a tropical zebra danio fish (*Brachydanio rerio*), genetically engineered with the red fluorescence gene of a sea anemone causing it to glow red under ultraviolet light.[280] The GloFish was introduced to the U.S. market in January 2004 by Yorktown Technologies of Austin, Texas, which claimed that it needed no federal permit prior to product marketing.[281] This novelty fish is sold for aquarium use throughout the United States, except in California, where it is banned.[282]

Environmental groups protested the sale of the GloFish, labeling them "frankenfish," and predicted that their sale "opens the dams to a whole host of nonfood genetically engineered organisms."[283] The Center for Food Safety claimed that, "Allowing the unregulated sale of GloFish

279. *See* Bratspies, *supra* note 152, at 457–58.

280. The genetically modified fish is marketed under the names "Night Pearl Glo Fish" or "TK-1" by the Taikong Corporation of Taiwan. *See* Taikong Corp., Select Version, http://www.azoo.com.tw/select.html (last visited April 9, 2007). In 2002, Taiwan became the first country to authorize sales of a genetically modified organism as a pet. In 2005, Taikong claimed that it would "announce 5 new species Fluorescent Fish at the same time." Taikong Corp., The Announcement of 5 New Species Fluorescent Fish and Neon Coral Aquarium, http://www.azoo.com.tw/azoo_en/modules.php?name=News&new_topic=15 (last visited Jan. 19, 2007). Reportedly, 100,000 of the glowing fish were sold in less than a month at $18.60 each. Wikipedia, GloFish: Fact Index, http://www.fact-index.com/g/gl/glofish.html (last visited April 9, 2007).

281. Press Release, Ctr. for Food Safety, Lawsuit Filed to Block Sale of First Genetically Engineered Pet Fish (Jan. 14, 2004), *available at* http://www.centerforfoodsafety.org/cfs_sues_f.cfm; Bratspies, *supra* note 152, at 467.

282. *See* Kenneth R. Weiss, *In Reversal, FDA Says It Will Not Regulate Bioengineered Fish*, L.A. TIMES, Dec. 10, 2003, at A31. The importer of the GloFish was denied an exemption by the California Fish and Game Commission on December 3, 2003. The commission later required that, for an exemption, Yorktown would need to complete an environmental impact report as required by the California Environmental Quality Act. *See* Bratspies, *supra* note 152, at 458 & n.5 and surrounding discussion; *see also* Steve Nash, *For Whom the Fish Glow: California Rejects GloFish, but the FDA Says, 'Let Them Swim,'* SFGATE.COM, Jan. 11, 2004, http://sfgate.com/cgi-bin/article.cgi?file=/c/a/2004/01/11/INGHT44JFU1.DTL. California prohibits the import or sale of transgenic fish without a permit or an exemption for fish in biomedical laboratories that can ensure the fish will not escape into the wild. CAL. CODE REGS. tit. 14, § 671 (2006).

283. Wikipedia, Glofish, http://en.wikipedia.org/wiki/Glofish (last visited Feb. 7, 2007) (quoting Joseph Mendelson, Legal Director, Center for Food Safety); *see also* Weiss, *supra* note 282; Dan Bacher, *From GloFish to Frankenfish*, COUNTERPUNCH, Dec. 30, 2003, http://www.counterpunch.org/bacher12302003.html.

provides a gateway for genetically engineered fish to find their way onto our dinner plates and into our environment."[284]

However, despite this opposition to the GloFish, the FDA declared:

> Because tropical aquarium fish are not used for food purposes, they pose no threat to the food supply. There is no evidence that these genetically engineered zebra danio fish pose any more threat to the environment than their unmodified counterparts which have long 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.[285]

Although the FDA is the lead agency for the regulation of transgenic animals, instead of scrutinizing the first transgenic animal offered for sale to the public or requiring permit or regulatory approval before marketing, the FDA allowed the GloFish to enter into interstate commerce wholly unregulated.[286]

The FDA's decision closely followed the intended-use focus of the Coordinated Framework and of the FDCA. The intended use of the fish was as an aquarium "pet," and thus was expected to be isolated from ecosystems, and not to be eaten by people or livestock. This expectation ignores the fact that the GloFish is visibly different from its natural counterparts, and that, as a living creature, the fish presents the possibility of escape or release followed by uncontrolled breeding. Thus, the fish might enter the environment and the food chain. Repeated experiences in which pets released by their owners into public areas have wrecked havoc on the ecosystem, and even threaten the safety of people in the area, demonstrate the shortsightedness of assuming a creature will remain in its intended setting after sale.[287] Nevertheless, the FDA concluded that this unprecedented life form would have to pose a clear threat to public health before it would be afforded any real scrutiny. Such willful disregard of a demonstrated potential for risk implicates the foundational assumptions of the Coordinated Framework and the FDCA.

Environmental groups filed suit to block the sale of the GloFish, seeking declaratory relief stating that the GloFish are subject to federal

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284. Press Release, Ctr. for Food Safety, *supra* note 281.

285. FDA, Statement Regarding Glofish, *supra* note 130.

286. *See* Bratspies, *supra* note 152, at 459.

287. *See* Edward L. Mills et al., *Exotic Species and the Integrity of the Great Lakes: Lessons from the Past*, 44 BIOSCIENCE 666 (1994) (reporting that "one of the most pervasive and damaging anthropogenic impacts on the world's ecosystems, including the Great Lakes, is the introduction of nonindigenous species" such as through the discarding of pets into the environment); Amitabh Avasthi, *Releasing Nemo Proves a Disaster for Native Fish*, NEW SCIENTIST, July 3, 2004, at 13 (explaining that exotic predatory fish and other ornamental fish thought to have been released by careless aquarium owners are appearing off the U.S. coast and could harm fisheries, introduce parasites, and endanger native species).

regulation and cannot be sold further without proper approvals.[288] In March 2006, the District Court of the District of Columbia deferred to the FDA, affirming the agency's discretion to decide not to regulate the commercial sale of the GloFish.[289] As plaintiff, the International Center for Technology Assessment claimed that although the GloFish is intended for use in home aquariums, the fish "could be put to other uses and readily enter the animal and human food chains through accidental or intentional releases."[290] Nonetheless, the FDA focused on the intended use of these fish as pets, rather than as food or drugs, and the presumption of safety for GMOs in its determination not to "regulate these particular fish."[291]

The court twice dismissed all of the plaintiffs' claims—in the original proceeding and on rehearing. The first two claims alleged that the FDA improperly refused to regulate the GloFish, and that the FDA's failure to assert regulatory authority over the GloFish violates the New Animal Drug Application (NADA) provisions of the FDCA.[292] The court held that the FDA's "enforcement decisions relating to unapproved new animal drug products are discretionary and are not subject to judicial review under the [Administrative Procedure Act]."[293] The plaintiffs claimed that the FDA was mistaken in asserting that the agency lacked 'discretion over GMOs without intended food or drug uses.[294] The court denied the motion to amend its previous judgment, explaining that, because "plaintiffs could not show that Yorktown submitted a NADA, . . . there were no statutory 'guidelines for the agency to follow in exercising its enforcement power,' and accordingly, the court did not have jurisdiction to review the claim."[295] Plaintiffs' National Environmental Policy Act claims were also dismissed because the decision not to regulate was not considered a major federal action upon which to base a challenge.[296]

The district court deferred to agency decision making and expertise,[297] explaining that, "Generally, an agency's decision not to prosecute or enforce is committed to the agency's discretion and courts

288. *See* Int'l Ctr. for Tech. Assessment v. Thompson, 421 F. Supp. 2d 1, 5 (D.D.C. 2006); *see also* Press Release, Ctr. for Food Safety, *supra* note 281; Wikipedia, Glofish, *supra* note 283.

289. *ICTA*, 421 F. Supp. 2d 1.

290. *Id.* at 4.

291. *See* FDA, Statement Regarding Glofish, *supra* note 130.

292. *ICTA*, 421 F. Supp. 2d 1 at 5–6.

293. *Id.* at 8.

294. *Id.* at 6.

295. *Id.* at 7–8 (quoting the court's own previous memorandum opinion).

296. *See id.* at 9–10.

297. *See id.* at 7–8; *see also* Alliance for Bio-Integrity v. Shalala, 116 F. Supp. 2d 166 (D.D.C. 2000) (deferring to the agency determination that the genetically modified product be generally recognized as safe).

presumptively do not have subject-matter jurisdiction to review actions committed to agency discretion," unless "the agency refuses to institute proceedings based on the mistaken belief that it lacks jurisdiction."[298] Under this limited standard of judicial review of agency decision making, the court held that plaintiffs had failed to show that amendment of the previous order was necessary because of an intervening change of controlling law, new evidence, or the need to correct a clear legal error to prevent a manifest injustice.[299]

The court did not directly consider whether the FDA had authority to regulate the GloFish or whether the agency's decision was truly based on a perceived lack of authority. Instead, the court avoided this question and based its consideration on an evidentiary finding. The court explained that "the evidence available, the GloFish statement, states that the FDA 'finds no reason to regulate' GloFish . . . . Nowhere does the statement indicate that the FDA believed it did not have the authority to regulate GloFish."[300] As the court had previously stated in the initial dismissal of the claim, the "FDA is simply exercising its discretion not to take enforcement actions against these particular fish."[301]

This case demonstrates how difficult it is to successfully challenge an agency decision, based both on the deferential standard of judicial review and the substantial evidentiary hurdles. Thus, it is best that controlling agencies adopt strong, clear standards for the regulation of GM products of all sorts, whether through statute, regulation, or agency guidance.

### *2. Glow-Pigs?: Green Fluorescent Protein Pigs*

In December 2005, scientists from National Taiwan University's Department of Animal Science and Technology announced that, similar to the process for the GloFish, they had introduced green fluorescent protein (GFP) genetic material from jellyfish into pig embryos to create three green, glow-in-the-dark pigs.[302] In daylight, the researchers say the pigs' eyes, teeth and hooves appear green, and the skin has a greenish tinge. In the dark, under black light, they glow bright green.[303] According to Professor Wu Shinn-Chih, one of the creators, "There are partially

298. Int'l Ctr. for Tech. Assessment v. Thompson, 421 F. Supp. 2d 1, 6 n.2 (D.D.C. 2006).

299. *See id.* at 6–11.

300. *Id.* at 6–7.

301. *Id.*

302. *See* Bill Mouland, *How Green Pigs Hog the Limelight*, DAILY MAIL (London), Jan. 13, 2006, at 11 (announcing the creation of three transgenic pigs by Taiwanese scientists through the introduction of Green Fluorescent Protein from jellyfish into pig genes); *see also* Chris Hogg, *Taiwan Breeds Green-Glowing Pigs*, BBC NEWS (Hong Kong), Jan. 12, 2006, http://news.bbc.co.uk/go/pr/fr/-/1/hi/world/asia-pacific/4605202.stm; *Taiwanese Researchers Breed Glowing Pigs*, S.F. CHRON., Jan. 13, 2006, *available at* http://www.sfgate.com/cgi-bin/article.cgi?file=/news/archive/2006/01/13/international/i131540S11.DTL.

303. *See* Hogg, *supra* note 302.

fluorescent green pigs elsewhere, but ours are the only ones in the world that are green from inside out."[304] As Wu described, "[e]ven their hearts and internal organs are green."[305]

According to the creators, the pigs are intended to be used in stem cell research and in the study of human disease. Professor Wu claims that the green pigs are intended to help researchers monitor and trace tissue changes during physical development.[306] The pig's genetic material encodes a protein that glows green under fluorescent light into every cell in the animal. This allows researchers to inject the GFP pig cells into other animals and then track the progress of those cells without need for biopsy or invasive tests.[307] The Taiwanese scientists say that although the pigs are green and glow, they are otherwise no different from any others.[308] The researchers hope the green pigs will mate with ordinary female pigs to create the next generation of green pigs, eventually breeding numerous transgenic pigs for use in research.[309]

No move has yet been made to introduce the GFP pigs to the United States for any purpose and the FDA has not commented on the green pigs. Although the Taiwanese pigs are the first wholly green transgenic creations, green fluorescent protein and its mutant relative, yellow fluorescent protein, have been used in biomedical research in the United States and throughout the world for several years. Scientists created a partially glow-in-the-dark rabbit in 2000,[310] a nude, transgenic green mouse in 2004,[311] and a mosquito with glowing testicles in 2005.[312]

The GFP pig illustrates problems of the FDCA and Coordinated Framework related to their excessive focus on the specific comparison risk determination tool, the weaknesses of allowing intended use to drive regulatory oversight, and the inability to address environmental risks without a direct link to public health. No mention has yet been made of the use of the green pigs, or their progeny, as either food or as pets, but the potential desire to commercialize the pigs for these uses is obvious.

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304. Mouland, *supra* note 302.

305. *Id.*

306. *See* Hogg, *supra* note 302.

307. *See id.*

308. *See id.*

309. *See id.*

310. *See* Tom Abate, *News Stories About Tinkering With DNA Miss the Big Picture: Glowing Rabbit Shows We're Creeping Toward Redesigning Human Life*, S.F. CHRON., Sept. 25, 2000, at D-1; Kristen Philipkoski, *RIP: Alba, The Glowing Bunny*, WIRED NEWS, Aug. 12, 2002, http://www.wired.com/news/medtech/0,1286,54399,00.html.

311. Meng Yang et al., *Transgenic Nude Mouse with Ubiquitous Green Fluorescent Protein Expression as a Host for Human Tumors*, 64 CANCER RESEARCH 8651 (2004).

312. *See* Press Release, Imperial College London, New GM Mosquito Sexing Technique Is Step Towards Malaria Control, Report Scientists (Oct. 9, 2005), *available at* http://www.ic.ac.uk/P6929.htm.

Who doesn't think about green ham (and eggs) when considering green pigs?[313]

Under the current regulatory scheme, should the developer propose to import the green pigs to the United States for uses other than food or drugs—perhaps as pets or for industrial purposes—the FDA could treat the pigs just like the GloFish and find no reason to regulate the transgenic pigs since they pose no clear threat to public health.[314] Thus, the transgenic pigs would be regulated under no more scrutiny than normal pigs and their products receive. Under the specific comparison review, the only physical difference between the green pigs and regular pigs is the presence of GFP. Consequently, only the GFP requires risk analysis, and since GFP has not been proven to cause any risk in itself, there is no need for additional scrutiny of the pig. So long as GFP is not found to pose risks of toxicity or allergenicity, the green pigs may also qualify for food use. However, if the creator promotes the pig for medical use, the cells derived from the pigs for this purpose would be subject to the strict drug approval regime.

Despite the Coordinated Framework's goals to increase cooperation between agencies and to make the product review process more clear and efficient for industry, the Coordinated Framework actually creates a cumbersome and ineffective process that requires much duplication of effort. For a product like the GFP pig, which poses the potential for many differing intended uses, the responsible regulatory agencies likely must repeat the basic analysis of the pig and its differences from conventional pigs for each use that requires a different standard of review. In addition, a strong possibility exists that the pigs, once introduced into the commercial marketplace, will be used for purposes other than those for which they were specifically considered and approved.

The absence of clear authority to address environmental risks that do not directly affect the health of people or livestock presents a further regulatory obstacle. Should it turn out, for example, that GFP pig scat harms dependant insect life, thus damaging the ecosystem, the FDA may not have the authority or incentive to remove the pig from the marketplace.[315] Without FDA leadership, the burden of proving any

313. *See* DR. SEUSS, GREEN EGGS AND HAM (1960).

314. *See supra* note 285 and surrounding discussion.

315. Possible results of the consumption of GFP in pig scat by insects could include toxicity, digestability or nutrient delivery impacts, caused by the foreign protein, or transfer of the GFP to the insect genes. However, these concerns are unsupported by any identified research in relation to GFP. No studies of these possible impacts on insects were identified, although there are studies of the consumption of GFP by mice and rats. *See* U. Hohlweg & W. Doerfler, *On the Fate of Plant or Other Foreign Genes upon the Uptake in Food or After Intramuscular Injection in Mice*, 265 MOLECULAR GENETICS & GENOMICS 225 (2001) (explaining that mice continuously fed daily with GFP DNA for eight generations, then examined by assaying DNA isolated from tail tips and internal organs, resulted in uniformly negative findings of any

hazard to people, animals, or the environment falls largely to nongovernmental actors, such as consumer groups, environmental groups, and academics, to develop and present adequate evidence to prove that the transgenic pig requires scrutiny beyond review of the green fluorescent protein itself.

Under the existing regulatory system, commercial production of the GFP pig would likely win regulatory approval. The FDA would consider the setting in which the GFP pig would be raised, the likelihood of escape, the ability to recall a defective product, and the lack of any specific evidence of risk. Pigs are generally raised in enclosed settings. Even if the GFP pig was to be raised as a trendy new pet, the pig would be unlikely to roam free. The pigs would be relatively contained in the home, and could be maintained separately from other pigs should the regulatory agencies so require. There is little risk of escape into the wild for a pet pig, although it is possible that dissatisfied owners might release their GFP pigs into the wild.

Without any evidence to show that the GFP pig is physically different from other pigs, the focus of regulatory scrutiny would be on the green fluorescent protein itself. Although different uses of GFP pig products would require different forms of regulatory review, the various regulatory units are not prevented from sharing their analytical data, rather than generating it anew for each forum of review.[316] Under the Coordinated Framework, proof that any difference between the GFP pig and traditional pigs is caused by the introduction of the green fluorescent protein would be required before the product could be rejected due to its transgenic nature. By allowing products without proven risk to enter the market, the regulatory agencies promote commerce and industry, while retaining the ability to recall and disapprove any product proven hazardous later. Arguably, any environmental impacts caused by the pig that do not directly impact public health are an issue for Congress to address should the traditional enforcement mechanisms of the EPA prove inadequate.

While the factors favoring commercialization of the GFP pig seem reasonable, they set a high threshold of proof for critics to prove that the

germline transfer of the orally administered DNA); *see also* Harold A. Richards et al., *Safety Assessment of Recombinant Green Fluorescent Protein Orally Administered to Weaned Rats*, 133 J. NUTRITION 1909 (2003) (examining the allergenicity and toxicity impacts of feeding pure GFP and transgenic canola expressing GFP to young male rats for twenty-six days to evaluate the potential toxicity and allergenicity). The Richards study found that ingestion of GFP did not affect growth, food intake, relative weight of intestine or other organs, or activities of liver enzymes, and the GFP rapidly degraded during simulated gastric digestion. The researchers concluded that GFP presents a low allergenicity risk and is not likely to represent a health risk to the rats or to humans.

316. This statement may have implications for agency agreements to maintain manufacturer application and voluntary consultation data as confidential. *See supra* note 274.

GFP caused a physical difference between the conventional and transgenic organisms. As the GloFish litigation demonstrated, the ability to overturn an agency decision is extremely limited, making the effectiveness of the agency's review process especially important. Waiting for Congress to pass new legislation to specifically address the uncertain environmental risks presented by current and future GMOs is an unlikely option due both to the uncertainty of the risks presented by various GMOs and the anti-business light in which environmental regulation often is viewed.

Crossover of novel genetic animals into the human or animal food arena has not yet occurred, but the first approvals are under FDA consideration.[317] Effective regulatory oversight will require the FDA to take a macroscopic view of the risks presented by the novel transgenic organisms, including the ability to identify and review broad evidence of risk as a part of the product approval process.

### *3. Transgenic Salmon*

Just as the GloFish was the first transgenic creature to be commercially marketed in the United States, transgenic fish is most likely to become the first commercially marketed transgenic animal marketed in the United States for food purposes.[318] The fastest growing aquaculture sector involves raising high-demand, and therefore high-value, fish for western food markets. Correspondingly, the vast majority of aquaculture research has been devoted to modifying these fish to better suit them for aquaculture.[319]

Fish grown in aquaculture systems attract significant genetic engineering research attention for several reasons. First, there is a growing demand for more aquaculture products, particularly in light of decreasing availability of wild fish populations.[320] Second, because fish lay eggs in large quantities, and those eggs are more easily manipulated than mammalian eggs, it is easier for scientists to insert novel DNA into the fish eggs to create transgenic food animals, than it would be to modify and reinsert the eggs of terrestrial livestock.[321] Research and development efforts in aquaculture have focused on accelerating growth rates and increasing efficiency of food conversion, disease resistance, or cold tolerance for farmed salmon or other food fish.[322] By inserting additional copies of fish growth hormone genes and mammalian promoters,

317. *See infra* note 318 and surrounding discussion.
318. *See* PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, *supra* note 227, at 6.
319. Bratspies, *supra* note 152, at 468.
320. *See* PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, *supra* note 227, at 4.
321. *See id.*
322. *See* Bratspies, *supra* note 152, at 469 n.46, 501.

researchers are able to accelerate fish growth rates such that modified fish grow from two to eleven times faster than their natural counterparts.[323] Endowed with these transgenic characteristics, the GM fish offer the prospect of more efficient and less expensive commercial production.[324]

As of 2002, researchers had genetically modified at least fourteen fish species to enhance their growth, including several species of carp, trout, and salmon, as well as channel catfish, loach, tilapia, and pike.[325] In 2003, the Food and Agriculture Organization of the United Nations reported twenty-three aquatic transgenic species in development.[326] The FDA is now reviewing proposals for the commercialization of several GM fish, in particular the Atlantic salmon.[327]

Unfortunately, the factors that make the transgenic fish attractive for aquaculture—rapid growth, super-normal resistances and tolerances—can pose serious risks to conventionally bred wild relatives, as well as to entire ecosystems, if these fish were to escape from their pens.[328] For the GM fish, escape is not just speculative, but has been shown in several studies to be a certainty under current containment measures.[329] Farmed fish are often contained in fish cages, traditionally suspended in open water. Ordinary wear and tear on the equipment and damage from storms or predators are reported to have allowed millions of farmed fish to escape, sometimes as many as several hundred thousand at one time.[330]

Once the GM fish escape, they may pose a threat to the ecosystem similar to an invasive species.[331] The narrow mandate of the substantial equivalence–based risk analysis imposed on the FDA does not include adequate assessment of risks that manifest outside of the identified physical differences in proteins.[332] When there is a risk of escape, other

323. *See* PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, *supra* note 227, at 7–8.

324. *See id.* at 7.

325. *See id.* at 5.

326. Bratspies, *supra* note 152, at 469.

327. *See* Justin Gillis, *Old Laws, New Fish; Environmental Regulation of Gene-Altered Foods Is a Gray Area*, WASH. POST, Jan. 15, 2003, at E01 (describing the Aqua Bounty effort to gain FDA approval of its GM Atlantic salmon).

328. Bratspies, *supra* note 152, at 470.

329. *See, e.g.*, PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, *supra* note 227 (concluding that the risks to the environment due to ineffective containment measures are extreme); NETHERLANDS COMM'N ON GENETIC MODIFICATION (COGEM), TRANSGENIC SALMON, A SAFE PRODUCT? ENVIRONMENTAL RISKS ASSOCIATED WITH THE PRODUCTION OF TRANSGENIC SALMON (2003), *available at* www.cogem.net/pdfdb/advies/CGM031124-01uk.pdf (finding that the risks due to escape of GM salmon are unacceptably large unless such efforts as rearing the fish on land with extensive containment measures are taken); NAT'L RESEARCH COUNCIL, *supra* note 278 (urging caution in the commercialization of GM fish due to tremendous uncertainty about nature and impact of risks).

330. *See* COGEM, *supra* note 329, at 15.

331. *See generally* Mills, *supra* note 287.

332. *See supra* Part IV.A.

relevant harms include indirect impacts on related species, latent harm (developing long after FDA review has concluded), harm to competitive species, and harm to the ecosystem from resource depletion or pollution from the GM entity. Evidence shows that the escapees eventually enter rivers to spawn, potentially causing genes from farmed fish to flow to wild relatives.[333] Concerns about escape vary depending on the number of fish that escape, their genetic composition and fitness, as well as the ecosystems they enter, and the fish populations already in those ecosystems.[334]

While improvements to containment measures are possible, such changes are likely costly. Some scientists suggest that state or federal authorities require transgenic fish grown in net pens to be sterile, to reduce the ability of transgenic fish to pass on their novel genes to wild relatives.[335] However, even sterile fish pose certain threats to wild fish populations due to competition to breed (unsuccessfully) and for food.

In 2003, the Pew Initiative on Food & Biotechnology released a report containing its assessment of the risks posed by the escape of transgenic fish.[336] The Pew report explains that the greatest risks posed by transgenic fish appear to derive from the escape of farmed fish into the wild. Escapes of farmed fish in large numbers are common, posing significant threat to aquatic biodiversity.[337] The escaped farmed fish run the risk of swamping the wild fish populations because of the large numbers of fish that might escape at one time.[338] The transgenic fish may also out-compete the conventional species for food or for the opportunity to breed. Some of the lines of transgenic salmon raised in the laboratory grow as much as four to six times faster than conventional salmon.[339]

The Pew report poses several models under which transgenic fish can affect a wild fish population following escape from containment. Under the "Spread Scenario," if the net fitness of a transgenic fish is equal to or higher than the net fitness of a conventional fish, gene flow is likely to occur and the genes of the transgenic fish will spread through the wild population, eliminating the wholly conventional fish population over time.[340] The "Trojan Gene" scenario suggests that the introduction of transgenic fish with enhanced mating success but reduced adult viability into a wild population could result in a rapid decline of the wild population. While the mating advantage of the larger GM fish spreads

333. *See* PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, *supra* note 227, at 18.
334. *See id.*
335. *See id.*
336. *See id.*
337. *See id.*
338. *See id.* at 26.
339. *See* NAT'L RESEARCH COUNCIL, *supra* note 278, at 11.
340. *See* PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, *supra* note 227, at 21.

the Trojan gene throughout the wild population, each successive generation would suffer from the reduced viability rates, "eat[ing] away at the population size."[341] The Pew study poses another scenario in which vital transgenic fish with limited breeding success out-compete more fertile suitors, and quickly drive down the fish population through reduced reproductive rates.[342] In the end, the escaped GM fish may or may not be successful in out-breeding the wild fish, but both successful breeding of flawed progeny and failure to reproduce can have severely deleterious impacts on the wild fish population.[343]

The Pew report concludes that the regulatory framework for the cultivation of GM fish should be based upon reliable, objective criteria that consider the risks of transgenic fish in a more realistic and reliable way than previously has been the case.[344] All of the risks presented by the GM fish must be analyzed and quantified, including threats to biodiversity. The Pew report supports the use of sterile fish for production purposes in order to considerably reduce risks to biodiversity.[345] However, the Pew report questions the authority of the FDA to regulate environmental threats under the FDCA[346]—lending further support to the concept that the FDA must clearly expand its view of GM risks to include environmental implications, either through agency reinterpretation of existing authority or through new legislation.

The National Research Council (NRC) also strongly supports the drive for broader review of the risks of GM animals. In evaluating animal biotechnology for the FDA, the NRC found that sufficient "gaps still exist in our understanding of the key net fitness parameters to allow an assessment of the impact of [the escape of GM Atlantic salmon] into the wild."[347] The NRC explained that there is an unavoidable environmental concern about the potential for evolutionary change due to the commingling of GM fish with wild species, because "the magnitude of phenotypic change that is possible with transgenesis could exceed that of conventional breeding or natural mutations."[348] Thus, the faster-growing salmon made possible by the growth hormone gene enhancement create an environmental risk that escaped salmon could interbreed with the wild salmon and alter the entire species.[349] The magnitude of the escape problem prompted the NRC to call for caution regarding

341. *Id.* at 22.
342. *See id.*
343. *See id.* at 20.
344. *See id.* at 59–60.
345. *See id.* at 27.
346. *See id.* at 49.
347. *See* NAT'L RESEARCH COUNCIL, *supra* note 278, at 11.
348. *See id.* at 79.
349. *See id.* at 11.

experimentation and commercialization of transgenic fish—due both to the certainty of escape and the risks posed by the transgenic fish loose in the ecosystem.[350] The NRC concluded that the uncertainty in risk identification and quantification prevented an informed determination of the proper course regarding the commercialization of transgenic fish.[351]

Despite the intention of the Coordinated Framework to promote effective regulation, and the asserted adequacy of existing FDCA statutes, the FDA has yet to figure out how to regulate transgenic animals. The agency announced plans to release guidelines on transgenic animals intended for food use in 2001. But the biotechnology industry is still waiting.[352]

The Coordinated Framework's rejection of the potential need for statutory change places regulatory agencies in a very difficult position when technology prompts unforeseen repercussions. The agencies are unable to adopt guidance that conflicts with existing law and must manipulate existing law through tortured interpretations to address unavoidable complications. For example, in the absence of any guidelines regarding transgenic animals intended for food use, the FDA uses its new animal drug (NAD) approval authority to regulate transgenic fish. This is based on the concept that the transgenic protein affects the "structure and function" of the recipient animal in a manner analogous to that of a veterinary drug.[353] Unfortunately, this NAD authority may not apply to changes in the structure and the function of the conventional fish whose environment is impacted by the escape of GM fish. The FDA is left ill advised as to how to proceed in the face of the uncertain, but likely very high, potential for harm to aquatic environments due to the introduction of transgenic fish. Not only does the FDCA provide weak authority for regulating animal biotechnology, but FDA's institutional capacity to assess and handle the variety of hazards posed by transgenic fish and other animals is called into question.[354]

Perhaps the biotechnology industry itself has created a solution to regulatory uncertainty. In response to concerns about whether the FDA has the authority to appropriately regulate transgenic fish, Joseph McGonigle, vice president of business development for Aqua Bounty, a

350. *See id.* at 92; *see also* Bratspies, *supra* note 152, at 470.

351. *See* NAT'L RESEARCH COUNCIL, *supra* note 278, at 92.

352. *See* Andrew Martin, *Will FDA Bite on Genetically Modified Salmon?*, SEATTLE TIMES, Nov. 22, 2003, *available at* http://seattletimes.nwsource.com/html/home. As of January 1, 2007, the FDA had not issued guidance (or draft guidance) related to the growth of GM animals for food use. In December 2006, the FDA did release a risk assessment for cloned animal-based food products. However, the FDA specifically differentiated genetic engineering that involves the introduction of recombinant genetic material from cloning. *See supra* note 197 and surrounding discussion.

353. OSTP, GROWTH-ENHANCED SALMON, *supra* note 150, at 13–14.

354. *See* Bratspies, *supra* note 152, at 472.

major GM fish developer, responded, "I understand the argument, but as a practical matter, the FDA has asserted jurisdiction."[355] McGonigle explained, "The only way that's going to change is if somebody like me is stupid enough to sue them. I'm not going to do that."[356] So far as the desires of industry and the agency coincide, agency action is unlikely to be challenged by the regulatees—a less-than-ideal model for the administrative state. However, once these interests diverge, the FDA will need to have answers to the questions of authority, procedure, and expectations.

### C. *Biopharming*

Biopharming is a form of bioengineering in which plants are genetically engineered to produce pharmaceutical proteins and industrial chemicals that they do not produce naturally.[357] Biopharming makes use of wide crosses, such as the splicing of human and animal genes into plant DNA. The human genes coax the crop plants to produce proteins, which can then be extracted from the plants and turned into medicines.[358] The transgenic plants become "mini-factories" producing specific proteins novel to the plant that are then extracted, refined and used in pharmaceutical and industrial applications.[359] The resulting products are referred to as "plant-made pharmaceuticals" (PMPs).[360]

The first efforts in biopharming, sometimes called molecular farming, involved genetic modifications to tobacco and corn to produce monoclonal antibodies (MAbs), enzymes, lactoferrin, collagen, gelatin,

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355. *See* Gillis, *supra* note 327.

356. *See id.*

357. USDA, Glossary of Biotechnology Terms, http://www.csrees.usda.gov/nea/biotech/res/biotechnology_res_glossary.html (last visited Jan. 29, 2007); Aziz Elbehri, *Biopharming and the Food System: Examining the Potential Benefits and Risks*, 8 AGBIOFORUM 18 (2005), *available at* http://www.agbioforum.org/v8n1/v8n1a03-elbehri.pdf; PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, PHARMING THE FIELD: A LOOK AT THE BENEFITS AND RISKS OF BIOENGINEERING PLANTS TO PRODUCE PHARMACEUTICALS 1 (2002), *available at* http://pewagbiotech.org/events/0717/ConferenceReport.pdf (providing further definition and discussion of "pharma" activities).

358. *See* Paul Elias, *'Biopharming' Industry Making Quiet Comeback: USDA Applications Double in 12 Months*, ENQUIRER (Cincinnati), June 2, 2004, *available at* http://www.enquirer.com/editions/2004/06/02/biz_biz2pharm.html.

359. The same process is also used to create plants which bear proteins used for industrial purposes. While the crop growth will be overseen by APHIS, and any pesticidal components will be considered by the EPA, the FDA arguably does not have authority to approve industrial GM products, since they are neither foods nor drugs.

360. *See* Brent Zettl & Larry Holbrook, *Let There Be Light: Plant-Made Pharmaceuticals' New Home is Underground—The Next Generation of Upstream Production*, BIOPHARM INT'L, Nov. 1, 2004, http://www.biopharminternational.com/biopharm/article/articleDetail.jsp?id=134062&pageID=1&sk=&date= (providing an introduction and discussion of PMP production options). In this discussion, PMPs will include plant-made industrial chemicals not intended for pharmaceutical use.

and vaccines.[361] Known products of biopharming available in the market today include a topical contraceptive, growth hormones, blood coagulants and thinners, industrial enzymes, and vaccines.[362]

In 2005, the Animal and Plant Health Inspection Service (APHIS), a division of the USDA, received permit requests for 456.29 acres of pharmaceutical and industrial use biopharmed crops.[363] The demand for biopharm permits is growing. By the end of 2006, permits for a total of 797.50 acres had been granted or were being reviewed by APHIS.[364] The most common biopharmed crops grown in U.S. field trials are corn, tobacco, and rice.[365] Alfalfa, potato, safflower, soybean, sugarcane, and tomato are also being investigated as potential biopharm hosts.[366] Suitable host plants must be capable of relatively simple bioengineering and high protein production levels, as well as being able to accommodate standardized procedures for extracting the PMP from the plant tissues.[367]

The review of the biopharming industry underscores the need for the FDCA and the Coordinated Framework to identify and address all of the potential and known risks posed by GM crops. Demonstrated experience with escape of GMOs from containment, contamination of traditional foods with unapproved GMOs, and the failings of the regulatory agencies to track and supervise biopharming all point to a need for regulatory change.

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361. It is easier to grow proteins from corn than from the leafy tissues of plants. *See* Sabrina Wagner, *Final Word: Plant-Made Pharmaceuticals: Improved Product Quality and Potency are Two Key Reasons to Produce Therapeutic Proteins in Plants*, BIOPHARM INT'L, Aug. 1, 2004, http://www.biopharminternational.com/biopharm/article/articleDetail.jsp?id=114974. One challenge is the separation of corn for molecular farming from corn for food and feed production, as evidenced in the StarLink episode. *See* Rebecca M. Bratspies, *Myths of Voluntary Compliance: Lessons from the StarLink Corn Fiasco*, 27 WM. & MARY ENVTL. L. & POL'Y REV. 593 (2003).

362. *See* BILL FREESE, FRIENDS OF THE EARTH, MANUFACTURING DRUGS AND CHEMICALS IN CROPS: BIOPHARMING POSES NEW RISKS TO CONSUMERS, FARMERS, FOOD COMPANIES AND THE ENVIRONMENT 1 (2004), *available at* http://www.foe.org/camps/comm/safefood/biopharm/BIOPHARM_REPORT.pdf.

363. Animal & Plant Health Inspection Serv. (APHIS), USDA, Release Permits for Pharmaceuticals, Industrials, Value Added Proteins for Human Consumption, or for Phytoremediation Granted or Pending by APHIS, http://www.aphis.usda.gov/brs/ph_permits.html (last visited Jan. 20, 2007). This acreage does not reflect the total acres grown, since applications representing over 300 acres were withdrawn; ultimately, only eighty-two acres were actually planted, according to APHIS records. *See id.*

364. *Id.*

365. *See* P. Byrne, Colo. State Univ. Coop. Extension, Bio-pharming, http://www.ext.colostate.edu/pubs/crops/ 00307.html (last visited Jan. 29, 2007); *see also* FREESE, *supra* note 362, at 1.

366. *See* Byrne, *supra* note 365.

367. *See id.*

### 1. *Regulation of Biopharmed Crops*

Biopharmed crops initially are regulated by the USDA, through APHIS, which oversees the field trials through which PMPs are developed.[368] After years of field trials, once a PMP appears ready for product approval, the FDA enters the scene. The FDA limits its role to evaluation of the extracted pharmaceutical itself and initiates its review at the clinical trial stage.[369] This Part first discusses the flaws in FDA's regulation of PMPs, followed by the problems in APHIS' oversight of the biopharm crops themselves.

The FDA's approach is particularly flawed in its application to biopharmed products. The FDA has neither devised a clear structure for the regulation of PMPs between the interested agencies, nor established its own review procedures for PMPs. In 2005, the director of the Center for Food Safety and Applied Nutrition (CFSAN), an inter-agency working group, explained that the FDA and CFSAN were still "working to clarify authorities for regulating genetically engineered crops ordinarily used to produce food (e.g., corn), whether they are intended for food, pharmaceutical, or industrial use, and to make sure there are no gaps in protecting human health and the environment."[370] The CFSAN director further explained that, "[f]or crops in the field, however, there are particular issues to be addressed, [including] the disposition of the residual crop left over after a pharmaceutical is extracted."[371] In addition, the FDA has no clear protocol for allergenicity testing of PMPs, nor has it proposed such a protocol.[372] Instead, the FDA has settled for issuing nonbinding recommendations to industry.[373] Despite over a decade of field testing, not a single PMP has received FDA drug approval.[374]

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368. APHIS, Release Permits for Pharmaceuticals, *supra* note 363.

369. *See* Seto, *supra* note 253, at 458–59.

370. *See To Review the Benefits and Future Developments in Agriculture and Food Biotechnology: Hearing Before the U.S. Senate Comm. on Agriculture, Nutrition and Forestry*, 109th Cong. (2005) (statement of Robert E. Brackett, Director, Center for Food Safety and Applied Nutrition, USDA) [hereinafter Brackett statement], *available at* http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=109_senate_hearings&docid=f:22645.pdf.

371. *Id.* Despite recognition that the uses of crop residues are controversial, the FDA has not foreclosed the possibility of permitting dual use of biopharm crop residues for food or animal feed. *See* CTR. FOR BIOLOGICS EVALUATION AND RESEARCH (CBER), FDA, DRAFT GUIDANCE FOR INDUSTRY: DRUGS, BIOLOGICS, AND MEDICAL DEVICES DERIVED FROM BIOENGINEERED PLANTS FOR USE IN HUMANS AND ANIMALS (2002), *available at* www.fda.gov/cber/gdlns/bioplant.pdf; *see also* FREESE, *supra* note 362, at 3.

372. *See* CBER, DRAFT GUIDANCE FOR INDUSTRY, *supra* note 371.

373. *See* Brackett statement, *supra* note 370; *see also* CBER, DRAFT GUIDANCE FOR INDUSTRY, *supra* note 371.

374. In contrast, over one hundred biopharmaceuticals, including insulin, are manufactured using animal, bacterial and yeast cell cultures, a $41 billion industry, while others are extracted from animal or human tissues. FREESE, *supra* note 362, at 3.

The FDA's approach to regulating PMPs closely follows the presumptions of the Coordinated Framework. In keeping with the assumption that existing law is adequate to cover GM regulation, the FDA has not promulgated special drug safety regulations covering PMPs, and has taken a very narrow view of the potential risks presented by PMPs. The FDA explained in 2005 that its "focus would be on proteins new to such plants because FDA believes that any potential risk from the low level presence of such material in the food supply would be limited to the possibility that it would contain or consist of a new protein that might be an allergen or toxin."[375]

FDA regulation of PMPs is further inhibited by the need to classify each derivative of the GM plant as either a food, drug, or industrial product. By adhering to the food-drug distinction, the FDA takes a schizophrenic approach to the regulation of the individual biopharmed plant. The plant itself is subject to minimal scrutiny before being planted and during its growth cycle. Any PMP derived from this plant is then subject to intense scrutiny via the New Drug Approval process. Yet, any industrial-use chemical derived from the plant may not be subject to any FDA scrutiny, since it is neither a food nor a drug. The remainder of the plant, the residue, may then be compared to naturally derived plants of that variety under the food additive regulatory structure, if the plant residue is to be used for human or animal consumption. Such mixed scrutiny of the various aspects of a single transgenic organism highlights the irrationality of the single-product approach to FDA regulation. The FDA must force each intended use of a single organism into one of the available regulatory product definitions, which establishes the level of scrutiny to which each GM product will be subjected.

The potential for multiple reviews of a single organism, under differing levels of regulatory scrutiny, is inefficient because each review is likely to duplicate, at least in part, the efforts for another intended use. If the product reviews are performed by separate bureaus within an agency, such as review by both agricultural product experts and by drug experts, without cooperation between these units, no economies are gained from a shared learning curve nor is intra-agency communication utilized effectively. The product proponent is likely to have to answer overlapping inquiries from within a single agency. Such regulation is costly, slow, and inflexible—exactly the types of problems the Coordinated Framework was intended to address.

Experience shows that the initial regulation of biopharming by the USDA, through APHIS, is also very flawed. High-risk crops, such as those designed to produce pharmaceutical or industrial compounds and those modified with human genes, are subject to a permitting process

375. *See* Brackett statement, *supra* note 370.

managed by APHIS.[376] APHIS reviews permit applications on an ad hoc basis. However, there are no eligibility requirements and no performance standards to be met by potential PMP developers in the regulations for GM plants grown under APHIS permit.[377] In addition, in January 2006, the USDA Inspector General (IG) released a report highly critical of APHIS's efforts to control the growth of GM plants. The report concluded that the risk of escape and contamination remained unacceptably high.[378]

The primary conclusion of the USDA IG audit was that "APHIS lacks basic information about the field test sites it approves and is responsible for monitoring, including where and how the crops are being grown, and what becomes of them at the end of the field test."[379] The USDA IG found, "APHIS does not follow up with all permit and notification holders to find out exactly where the fields have been planted or if they have been planted at all."[380] In fact, in some cases, APHIS may only be aware of the state and county where an applicant plans to conduct a field test. Of the twenty-eight notification applications reviewed in the IG audit, none specifically identified the field site locations.[381] Although APHIS responded to this report with proposed improvements in the inspection and monitoring program,[382] it is reasonable to doubt that the full extent of both compliant and noncompliant biopharm experiments are being adequately tracked, reviewed, or regulated considering the USDA's history of lax monitoring standards and procedures, the limited staffing of field inspectors, and the USDA's organizational culture which focuses on the promotion of the U.S. agricultural industry.

The USDA IG audit comes six years after the StarLink corn fiasco, the largest GM food contamination incident in U.S. history. StarLink is a man-made corn variety, genetically engineered to produce Bt toxin, a pesticide toxic to some common crop pests.[383] Due to the nature of the genetic transformation involved in creating this corn variety, the FDA

376. APHIS, USDA, Introduction to Biotechnology Regulatory Services of the Animal & Plant Health Inspection Service, http://www.aphis.usda.gov/brs (last visited Jan. 30, 2007).

377. OFFICE OF INSPECTOR GEN., USDA, AUDIT REPORT: ANIMAL AND PLANT HEALTH INSPECTION SERVICE CONTROLS OVER ISSUANCE OF GENETICALLY ENGINEERED ORGANISM RELEASE PERMITS 3 (2005), *available at* http://www.usda.gov/oig/webdocs/50601-08-TE.pdf [hereinafter USDA IG REPORT 2005].

378. *Id.* at i.

379. *Id.* at i.

380. *Id.* at ii, 13.

381. *Id.* at 14–15.

382. *Id.* at v.

383. StarLink corn was genetically engineered to contain two novel genes—one conveying herbicide tolerance and one conveying insect resistance. Cry9C, the Bt protein incorporated into StarLink com, shared properties with some known food allergens. *See* Bratspies, *supra* note 13, at 386.

was uncertain about whether StarLink corn posed a risk as a human allergen. As a result, StarLink corn was not approved for use as human food. However, the manufacturer, Aventis CropScience, after assuring government regulators that the corn would be kept out of the human food supply, was able to gain a partial approval to produce and market StarLink corn for animal feed or industrial uses but not for human consumption.[384]

In September 2000, a coalition of environmental groups announced that they had discovered the prohibited StarLink corn in twenty-three common food products intended for human consumption.[385] The announcement lead to a series of product recalls, mass media attention, and consumer panic. Ultimately, the unapproved StarLink corn was discovered in more than 300 processed foods, each of which was pulled from grocery shelves around the world.[386] The USDA persuaded Aventis to repurchase the remaining StarLink corn from growers to ensure that no more of the unapproved corn entered the food supply. Under heavy pressure from the EPA, Aventis voluntarily withdrew StarLink's U.S. registration in October 2000.[387] Two years later, however, StarLink corn was still being found in corn shipments, and still roiling international markets.[388]

The StarLink crisis temporarily devastated U.S. grain exports.[389] The ultimate costs of the StarLink incident have been estimated at $100 million to over $1 billion.[390] In 2001, the *Toronto Star* reported that, "While reluctant to put a precise figure on the total cost of the StarLink controversy, [an industry consultant] said it could be 'potentially' more than $1 billion (U.S.) once all the lawsuits are settled."[391] While most of the cost was borne by Aventis, the USDA also took on part of the burden, and the GM industry as a whole faced a major setback in both U.S. and international markets.[392]

Because the environmental groups had identified the contamination before much of the unapproved corn had entered the food supply, the Centers for Disease Control and Prevention (CDC) and FDA eventually

384. *Id.*

385. *Id.*

386. *See id.* at 386–87; Bratspies, *supra* note 361, at 594.

387. *See* Bratspies, *supra* note 361, at 625.

388. *See id.* at 594–95.

389. *See id.* at 624; Bratspies, *supra* note 13, at 387.

390. *See* Mike Glover, *Biotech Corn Deal Reached*, SAN ANTONIO EXPRESS-NEWS, Jan. 24, 2001, at 3E; Stuart Laidlaw, *Starlink Fallout Could Cost Billions*, TORONTO STAR, Jan. 9, 2001, at Business 1; Bratspies, *supra* note 361, at 594, 624.

391. Laidlaw, *supra* note 390 (citing Don Westfall, Vice President of Promar International, a consulting company based in a Washington, D.C., suburb which published a report on the estimated costs of the StarLink incident).

392. *See* Bratspies, *supra* note 361, at 594.

concluded that there was a "low probability" that consumers would develop allergies to this corn.[393] Although there were mass reports of allergic reactions to the StarLink products following publication of the contamination, the CDC confirmed only a modest number of allergic reaction incidents.[394] The CDC conducted an epidemiological investigation of the reports of human illness associated with consumption of corn products containing the Bt protein,[395] concluding that twenty-eight of the fifty-one people submitting adverse event reports regarding ingestion of the StarLink corn had experienced apparent allergic reactions.[396] Most of these people reported multiple symptoms including loss of consciousness, weakness, or dizziness within one hour of product consumption. Nineteen individuals sought medical care, and two people were hospitalized. CDC identified no deaths or permanent injuries.

Importantly for the continuing regulation of GMOs, the CDC explained that "[e]valuating the public health implications from the inadvertent introduction of StarLink corn into the human food supply posed a challenging retrospective task."[397] The CDC concluded that the difficulties of its investigation highlighted the importance of evaluating the allergenic potential of GM foods before they become available for human consumption.[398]

Despite the enormous cost and public upheaval caused by the StarLink corn incident, APHIS did not improve its GM oversight processes in the years before the USDA IG audit. Instead, APHIS maintained wildly deficient crop supervision procedures and practices.[399] With such a poor mechanism in place to track the origin and extent of contamination once a GM product hazard is identified, it becomes even more important that the initial safety review for these products be as complete and thorough as possible.

### *2. Biopharming Advantages*

The manufacture of complex biopharmaceuticals via genetic manipulation in plants is an attractive alternative to conventional animal

393. *See* Bratspies, *supra* note 13, at 387.

394. *See* Bratspies, *supra* note 361, at 623, 628.

395. *See* CTRS. FOR DISEASE CONTROL & PREVENTION, INVESTIGATION OF HUMAN HEALTH EFFECTS ASSOCIATED WITH POTENTIAL EXPOSURE TO GENETICALLY MODIFIED CORN: A REPORT TO THE U.S. FOOD AND DRUG ADMINISTRATION 3 (2001), *available at* http://www.cdc.gov/nceh/ehhe/Cry9cReport/cry9creport.pdf.

396. *See id.* at 3, 5. The persons experiencing allergic reactions resided in fifteen states: California, Florida, Georgia, Illinois, Kansas, Maryland, Massachusetts, Missouri, New Jersey, North Carolina, Ohio, Texas, Virginia, Washington, and Wisconsin; and the District of Columbia and the Commonwealth of Puerto Rico. *See id.* at 6.

397. *Id.* at 10.

398. *See id.*

399. *See supra* note 378 and surrounding discussion.

cell culturing for the pharmaceutical company due to expected cost savings and production efficiencies.[400] Biotechnology companies have estimated that drug prices could fall by between ten and one hundred times due to the expected cost savings for infrastructure and production resulting from biopharming.[401] In addition, the natural properties of plants can lead to improved product quality and increased potency over animal cell alternatives,[402] and cultivation conditions in photosynthetic plant systems are much more flexible than in animal cell cultures.[403] Expression of pharmaceutical properties in seeds facilitates product recovery. An additional benefit for the biopharming industry is that PMPs may enable developers to avoid existing patent protections. For the farmer, the opportunity to grow a high-demand, potentially profitable, crop is economically attractive.[404]

However, there are many concerns over biopharm risks. In an editorial entitled "Drugs in Crops—the Unpalatable Truth," the editors of *Nature Biotechnology*, a leading industry journal state:

> [W]e should be concerned about the presence of a potentially toxic substance in food plants. After all, is this really so different from a conventional pharmaceutical or biopharmaceutical manufacturer packaging its pills in candy wrappers or flour bags or storing its compounds or production batches untended outside the perimeter fence?[405]

In response to these concerns, the number of biopharm field trials in the United States dropped sharply from a peak of forty-two in 2000 to just eight in 2003.[406] The reduction occurred in reaction to growing opposition from consumer groups, the food industry,[407] and scientists.[408]

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400. *See* Wagner, *supra* note 361.

401. *See* Seto, *supra* note 253, at 443, 453. For example, proteins that can be grown in corn which currently cost $1,000 per gram are estimated to cost between $10 (one hundred times less) and $100 (ten times less) per gram through biopharming. *See id.*

402. *See* Wagner, *supra* note 361.

403. *See id.* This flexibility is due to the wide ranges in temperature and pH, and low oxygen content, present in crop farming. These variations allow biotechnology companies to optimize the biopharm process according to protein requirements.

404. Of course, insurance costs, potential liability for containment breaches or product impurities or failures will heavily influence the fiscal appropriacy of growing biopharm crops.

405. Editorial, *Drugs in Crops—The Unpalatable Truth*, 22 NATURE BIOTECHNOLOGY 133 (2004).

406. Information Systems for Biotechnology, Field Test Releases in the U.S., at http://www.isb.vt.edu/CFDOCS/fieldtests1.cfm (last visited Jan. 27, 2007) (USDA's GM crop field trial website. Field test numbers were calculated by searching on "phenotypes" antibody, industrial enzyme(s), novel protein and pharmaceutical protein to identify the pharmaceutical or industrial crops. Date of permit application is denoted in the permit numbers.); *see also* FREESE, *supra* note 362, at 4.

407. *See* Press Release, Nat'l Food Processors Ass'n, No Use of Food or Feed Crops for Plant-Made Pharmaceutical Production Without A '100% Guarantee' Against Any Contamination, Says NFPA (Feb. 6, 2003) (on file with author).

However, the downward trend in biopharming appears to have reversed. In 2005, the number of field tests increased to fifteen, indicating a resurgence in the practice.[409] Biopharming is also being promoted in developing countries,[410] possibly to take advantage of weaker foreign drug regulation. Due to recent increases in investment in new facilities, capacity for biopharming within the United States is now growing as well.[411] Nonetheless, the risks of biopharming remain very important to the evaluation of this emerging technology.

### *3. Manufacturing Risks*

There are several safety factors that must be considered in the manufacture of PMPs. Largest among these are the risks of contamination to traditional crops and harvested products due to containment failures. This includes the inability to contain the GM plants themselves, to prevent gene flow into traditional plant populations, and the accidental contamination of traditional crop products with GM product.[412]

Crop containment is an important factor in the selection of plant species for manipulation. Pharmaceutical traits can spread naturally through seed or pollen dispersal by wind, rain runoff, birds, and animals. Critics of open-field biopharming argue that corn pollen can travel for miles on the wind, and insects can fertilize conventional crops with

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408. Geneticist and biochemist Dennis R. McCalla and colleagues point to potential health impacts from inadvertent consumption of plant-grown vaccines, stating that there is a "very high probability" of contamination to the human food supply from "plants engineered to produce pharmaceuticals, enzymes [and] industrial chemicals." MCCALLA ET AL., REGULATION OF GENETICALLY MODIFIED FOOD: A SUBMISSION TO THE CANADIAN BIOTECHNOLOGY ADVISORY COMMITTEE (2001). They conclude: "Only species that are not consumed by humans or by livestock should be permitted for the production of these substances." *Id. See also* FREESE, *supra* note 362, at 4.

409. Information Systems for Biotechnology, *supra* note 406; *see also* APHIS, FDA, Release Permits for Pharmaceuticals, *supra* note 363. *See generally* Molecularfarming.com, http://www.molecularfarming.com; http://www.molecularfarming.com/stats.html (last visited Jan. 30, 2007) (a database of farmers seeking to promote biopharming internationally).

410. *See, e.g.*, Int'l Serv. for the Acquisition of Agri-biotech Applications (ISAAA), http://www.isaaa.org/default.html (last visited Feb. 12, 2007). The ISAAA is a not-for-profit organization that delivers the new agricultural biotechnologies to the poor in developing countries. *See also* Molecularfarming.com, http://www.molecularfarming.com (last visited Jan. 30, 2007) (inviting farmers, in any nation whose regulations permit such activities, to join the Global Database if they are willing to train to become contract growers or to lease or sell suitable land to other GM crop growers.)

411. *See* Wagner, *supra* note 361; *see also* Elbehri, *supra* note 357, at 21 (discussing the expansion in the biopharm industry in recent years).

412. *See, e.g.*, PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, HAVE TRANSGENES, WILL TRAVEL: ISSUES RAISED BY GENE FLOW FROM GENETICALLY ENGINEERED CROPS (2003); Norman C. Ellstrand, *When Crop Transgenes Wander in California, Would We Worry?* 60 CAL. AGRIC. 116 (2006), *available at* http://repositories.cdlib.org/cgi/viewcontent.cgi?article=3106&context=anrcs/californiaagriculture.; Mandel, *supra* note 187, at 2194.

biopharm pollen.[413] Accidental human-caused dispersals also create containment failures, including the carrying of biopharm seed remainders to conventional fields by harvesting equipment and seed spillage in transit.[414] In addition, "volunteers"—unharvested seed that sprouts in seasons following the expected termination of the crop—are extremely difficult to control.

There have already been multiple containment failures of biopharmed crops in the United States, despite the limited application of biopharming to date. In 2002, biopharm industry leader, ProdiGene, Inc., was involved in two contamination incidents. In Nebraska, volunteer biopharm corn sprouted among soybeans planted in the same field the year after a biopharm experimental crop was grown, despite efforts to eradicate the biopharm crop at the end of the experiment.[415] Ultimately, 500,000 bushels of soybeans intended for food purposes were quarantined and then destroyed. In Iowa, biopharm corn cross-pollinated a neighboring field, resulting in destruction of 155 acres of potentially contaminated corn.[416] The risk of contamination increases commensurately when field trials of a few acres are followed by commercial plantings of hundreds or thousands of acres.

There are a variety of possible containment measures, including simple geographical separation such as patterned planting of incompatible crops, such as rice and safflower, to minimize the risk of GM plant cross-fertilization with conventional crops.[417] More complex options include: the expression of the biopharmed product in chloroplasts not transferred by pollen; use of airlift bioreactors for transgenic plant sprouting; and use of photobioreactors such as lemna (a free-floating aquatic plant) or moss to grow aquatic plants.[418] However, the National

413. *See* COMM. ON BIOLOGICAL CONFINEMENT OF GENETICALLY ENGINEERED ORGANISMS, NAT'L RESEARCH COUNCIL, BIOLOGICAL CONFINEMENT OF GENETICALLY ENGINEERED ORGANISMS 47, 61 (2004), *available at* http://www.nap.edu/catalog/10880.html. *But see* Seto, *supra* note 253, at 455–56 (positing that statistical data show that pollen spread contamination risks have been overestimated by the critics of biopharming).

414. *See* COMM. ON THE BIOLOGICAL CONFINEMENT OF GENETICALLY ENGINEERED ORGANISMS, *supra* note 413, at 35, 187.

415. *See* Bratspies, *supra* note 361, at 630.

416. *See* Mike Toner, *Alarms Sound Over 'Biopharming': Tainted Crops Cast Doubt on Gene Altering*, ATLANTA J. & CONST., Nov. 17, 2002, at 1C.

417. *See* Wagner, *supra* note 361.

418. *See id.* Each of these techniques either contains or prevents the distribution of plant material containing the PMP, so that it is not free to travel through the air, soil, or open water to an area where traditional plants are grown or where people or animals will unknowingly encounter and be exposed to the chemical. By preventing the PMP from entering the producer-plant's pollen, or by using a special hood to gather the PMP-containing pollen, or growing the PMP containing plant in an enclosed vessel, the risks of accidental exposure to the PMP is drastically reduced over normal crop growth and harvesting techniques.

Academy of Sciences concluded that total containment of pharmaceutical and other novel traits in field crops is virtually impossible.[419]

The containment risks of open-air biopharming can be reduced using newer, more contained biopharm techniques such as plant cell culturing and hydroponic cultivation.[420] These options allow complete control of growth conditions, more consistent drug quality, and easier purification than from whole-plant tissue. The anticancer drug, Taxol, is already grown in plant cell culture, and the cystic fibrosis drug "alpha-1-antitrypsin" has been successfully grown in rice cell cultures.[421]

Biopharming also presents special difficulties in gene containment. Non-GM crops fertilized with pollen from GM crops could produce seeds contaminated with GM genes. Gene containment mechanisms such as male sterility and chloroplast transformation are known to be "leaky"—some of the seeds produced remain fertile. For example, Avidin corn, a biopharm crop touted as male-sterile, was found to contain partially or fully fertile pollen in 18 percent of tested plants.[422] "Terminator" seed-sterility technology, designed to mitigate biopharm gene flow, presents technical flaws, potential health and environmental hazards, and would end the traditional practice of seed-saving.[423]

An additional risk presented by biopharm crops lies in the use and disposal of the residue of the plant once the PMP is extracted. Companies like ProdiGene have also proposed "dual use" of biopharm plants, in which the plant material is sold as food or animal feed after extraction of the drug or chemical.[424] Incomplete extraction would mean that drug or chemical residues remain in food products and feed, thereby entering the food chain.

The likelihood of containment failure, and of product contamination by unapproved GM crops, demonstrates how important it is that regulatory oversight of biopharming be improved. The many failings in the supervision of biopharm crop production, and review of the resulting

419. *See* COMM. ON THE BIOLOGICAL CONFINEMENT OF GENETICALLY ENGINEERED ORGANISMS, *supra* note 413, at 180, 182.

420. *See* Wendy Thai, *Recent Development: Transgenic Crops: The Good, the Bad, and the Laws*, 6 MINN. J. L. SCI. & TECH. 877, 892 (2005).

421. *See* FREESE, *supra* note 362, at 3; *see also* Stephan Hellwig et al., *Plant Cell Cultures for the Production of Recombinant Proteins*, 22 NATURE BIOTECHNOLOGY 1415 (2004), *available at* http://www.nature.com/nbt/journal/v22/n11/pdf/nbt1027.pdf.

422. *See* FRIENDS OF THE EARTH, BIOPHARMING: CASE STUDY OF AVIDIN CORN 2 (2002), *available at* http://www.foe.org/biopharm/csavidin.pdf.

423. *See* RICARDA A. STEINBRECHER, V-GURTS (TERMINATOR TECHNOLOGY): DESIGN, REALITY AND INHERENT RISKS TRANSFORMATION-INDUCED MUTATIONS IN TRANSGENIC CROP PLANTS 6 (2005), *available at* http://www.econexus.info/pdf/ENx-CBD-GURTs-2006.pdf; Michael Specter, *The Pharmageddon Riddle: Did Monsanto Just Want More Profits, or Did It Want to Save the World?*, NEW YORKER, Apr. 10, 2000, at 60, *available at* http://www.michaelspecter.com/pdf/pharmageddon.pdf.

424. *See* FREESE, *supra* note 362, at 2.

PMPs, must be addressed through the creation and maintenance of adequate regulatory processes.

### *4. Inherent Biopharm Risks*

In addition to the containment and contamination risks arising in the manufacture of biopharmed products, PMPs and plant-made industrial chemicals may pose additional risks in themselves—either to people directly, or through harm to the environment.

> Biopharmaceuticals usually elicit responses at low concentrations, and may be toxic at higher ones. Many have physiochemical properties that might cause them to persist in the environment or bioaccumulate in living organisms, possibly damaging non-target organisms . . . .[425]

Opponents of biopharming claim that the risks to humans inherent in biopharming may include: allergic reaction when plant-produced "human" proteins are perceived as foreign by the body, or through other exposure to biopharm produced allergens;[426] intentional or accidental exposure to super-active biopharmed drugs by inhalation, ingestion or skin absorption; crossover of engineered viruses between crops;[427] and side effects of biopharm drugs such as vitamin deficiency[428] or pancreatic disease in animals and possibly humans.[429] These side effects include the potential for immune system reaction to plant-specific sugar residues in biopharmed injectables such as insulin products.

In addition, the wide cross of animal genes into plant hosts for PMP production presents a heightened risk of viral contamination.[430] In traditional animal cell cultures, viral contamination of the pharmaceutical product is avoided through extensive virus removal procedures. Because no plant viruses are human-pathogenic, virus contamination is generally significantly less problematic for biopharmed plants.[431] However, the insertion of animal genes into plant DNA increases the possibility of viral contamination and the need for aggressive virus removal.

Biopharming can also pose important environmental risks. Direct ecological harms from open-air biopharming include harm to insects, such as from the production of digestion-inhibiting enzymes which would

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425. Glynis Giddings et al., *Transgenic Plants as Factories for Biopharmaceuticals*, 18 NATURE BIOTECHNOLOGY 1154 (2000).

426. For example, the trypsin and antitrypsin corn-grown industrial enzymes.

427. For example, Trichosanthin, an abortion-inducing drug which infects tomatoes, peppers, and other tobacco relatives, as well as the intended tobacco species.

428. For example, avidin-producing crops allegedly result in deficiencies of biotin, an essential B vitamin. *See* FREESE, *supra* note 362, at app. 2.

429. *See* FREESE, *supra* note 362, at 2. Aprotinin is alleged to cause pancreatic disease in animals and possibly humans.

430. *See* Wagner, *supra* note 361.

431. *See id.*

shorten the life or productivity of the insect.[432] Similarly, the biopharmed crop might produce proteins that specifically harm certain insect species.[433] Biopharm crops can also pose risks to the wildlife that eat them. All of these risks can be expected to increase as scientists learn how to generate increasingly higher concentrations of drugs and chemicals in these crops.[434] Finally, soil life may be harmed by biopharming because of root leakage that may persist in the soil for months after the crop is removed.[435] Effective regulatory oversight of biopharmed products and processes must consider these risks before environmental degradation occurs.

## VI. RECOMMENDATIONS FOR REGULATORY CHANGE

Now is the perfect time for the FDA to actively develop and promote a package of changes to modernize the Coordinated Framework, to interpret the FDCA to best reflect the needs of effective bioengineering regulation, and to pressure Congress for additional or revised statutory authority in those areas where existing law is inadequate. Recent developments in the biotechnology industry have illuminated the faults in the existing regulatory structure, especially in relation to wide-cross transgenics. This experience also outlines the regulatory needs of the future. The inability to fit novel transgenics into food and drug distinctions, the over-reliance on intended use to set regulatory scrutiny, and the uncertainty regarding how to approach environmental risks are all problems that can be quickly and cleanly addressed with relatively minor regulatory changes. The systemic problems surrounding the oversight of GM crop production and risk evaluation are also ripe for regulatory improvement. These issues are best addressed now, before the gaps and weaknesses in GM regulation are exposed through a catastrophic incident, such as the marketing of a hazardous GM product or the escape of an ecologically disastrous GM species. The modern era of novel transgenic development is just beginning, creating a terrific opportunity for the FDA and other agencies to establish a flexible and constructive regulatory structure upon which the industry can base its future development decisions.

To achieve this regulatory renovation, several recommendations for revisions to the Coordinated Framework and the FDCA are offered below. There are several avenues through which these recommendations can be implemented. Agencies, including the FDA, are able to implement

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432. *See* FREESE, *supra* note 362, at 2. Aprotinin is alleged to shorten the lives of honeybees and Avidin is alleged to kill or chronically impair at least twenty-six species of insects.

433. *See id.*

434. *See* Elbehri, *supra* note 357, at 24.

435. *See* Mandel, *supra* note 187, at 2199.

initial changes simply through a revision in their regulations and practices, although such change will require a corresponding update to agency assumptions, interpretations, and attitudes. Because assessment of the risks resulting from bioengineering is extremely technical, the courts and Congress will continue to defer to the decisions of the agencies with expertise in the field. Change to the Coordinated Framework itself will require coordination with the President's Office of Science and Technology Policy.

Other reforms to the FDCA will require legislative amendment. Although legislative amendment can be difficult to accomplish, recent changes in congressional membership indicate that the perspective of the new Congress may be more progressive, more environmentally oriented, and more open to modernizing the FDCA than was the case in previous years. The fact that regulation of transgenic products is a part of the essential government function of protecting the public welfare, and that the biotechnology industry is vital to the U.S. economy both support an FDA appeal for corrective legislation. The purposes of the Coordinated Framework—as expressed twenty years ago—to promote the biotechnology industry and to create an effective and efficient regulatory structure, will be furthered by these recommended changes, even as some of the assumptions of the original framework are rejected or revised.

### *A. Modifying the Basic Assumptions of the Coordinated Framework*

Agency experience in regulating GM products under the Coordinated Framework over the past twenty years has revealed serious weaknesses in the basic assumptions of the framework. The Coordinated Framework presumes that the laws that existed in 1986 are adequate to address the risks presented by modern and future transgenic innovations. It further presumes that the risks of genetic modification reside in the novel proteins inserted into an otherwise conventional organism. Therefore, risk assessment requires only a substantial equivalence comparison between the novel proteins and their conventional analogs.[436] The transgenic organisms are assumed to present no new risk in themselves. From this simple foundation, the Coordinated Framework has created a regulatory structure that is both inflexible and myopic with regard to the evolving needs for real GM regulation.

#### *1. Existing Law Does Not Suffice*

The assumption that existing laws provide adequate authority to regulate the risks posed by GM products is flawed. Existing law are excessively focused on the proponent's intended use of the GM product,

436. *See supra* note 184 and surrounding discussion.

and on a food-drug distinction that becomes increasingly difficult to draw as transgenics become more innovative. A reliance on laws developed long before the modern era of genetic modification creates a regulatory structure too inflexible to address the spectrum of unforeseen risk potentials presented by transgenic organisms and their derivatives. As discussed, these potential risks include environmental risks, latent risks developing long after the original product is marketed, and inherent changes to the structure or actions of the novel GMO that are not attributable to the specific proteins upon which regulatory scrutiny under the framework is required to focus. To remedy these problems, the Coordinated Framework must be revised to require a holistic review of the entire GMO and all of its potential impacts on the environment, its progeny, and the consumer who ultimately utilizes the GMO or its derivative products.

The Coordinated Framework must be changed to support the development of new law when existing statutes and regulations are shown to be inadequate for identified regulatory problems. The reliance on food and drug statutes and statutory definitions enacted long before genetic modification was foreseeable has been shown to be inadequate to address current technological realities.[437] The need for new law to adequately protect the public and the environment from harm must be balanced against the costs of any proposed restrictions and requirements incurred by the regulated entities and the regulatory agency. As a part of this new, open-minded attitude toward assessment of regulatory adequacy, the Coordinated Framework should support the prompt development of formal guidance documents, or preferably, the promulgation of regulations, to clarify the expectations and requirements of the agency for industry compliance. The FDA has failed to promulgate regulations to address technological developments in the biotechnology industry in recent years. Instead, FDA has issued several draft guidance documents that were not followed by the adoption of any formal guidance.[438] This has lead to an excessive reliance on voluntary industry participation in consultation processes—a weak and inconsistent structure for regulatory oversight.

In addition, by opening the door to agency efforts to seek legislative change, the FDA and the other agencies will no longer face a conflict between pursuing the best approach to biotechnology oversight and remaining faithful to the precepts of an inflexible and unchanging framework for regulation. This should inspire the agencies to more honestly assess the efficacy and adequacy of both their internal processes and the direction they give to regulated entities. Although the agencies

437. *See supra* note 76 and surrounding discussion.

438. *See supra* notes 108, 197, 372, and surrounding discussion.

cannot effect legislative change themselves, they can seek such change through their congressional oversight committees and other efforts to obtain congressional sponsorship for an agency-promoted bill.

### *2. Risk Assessment Must Be Comprehensive*

Next, the Coordinated Framework's presumption of safety for the products of genetic engineering, and the reliance on a specific comparison approach to risk assessment, must be revised. This system places far too great a burden on the opponents to a proposed GM product to provide evidence to the regulatory agency of physical harm caused by the product before a comprehensive safety review is triggered. Instead, the Coordinated Framework should adopt a holistic approach, in which all of the potential risks reasonably posed by a novel transgenic organism are considered prior to regulatory approval of the organism or product for commercial marketing. The assessment must include the potential harms to any ecosystem in which the organism might survive, whether or not the organism is intended to be introduced into that system, since escape is always a possibility. Containment measures must be appropriate to the level of risk the transgenic organism reasonably presents. The reasonable estimation of risk must involve the agencies' best estimates of inherent harms, harms to the environment, and latent or undiscovered risks likely to manifest in future years. Although such estimation involves quantification of uncertainty, such estimates are common in every field in which risk modeling is required. The FDA and the other agencies must rely on their scientific knowledge and experience in the field to create a discretionary assessment of risk, rather than simply rejecting risk based on the requirements of an outdated and unscientific framework.

The current method for risk assessment for GM products is a stovepipe approach, in which each product to be derived from a GMO is narrowly reviewed based on how the product is defined. Regulators are to review only that component of the GM product shown to be physically different from the conventional analog organism. This allows each organizational unit within the regulatory agencies to interpret the purview of its analysis very narrowly.

A single risk assessment for each innovative GMO, focusing on identifying all potential risks to humans, animals, plants, and the environment, offers the benefits of efficiency, reliability, and consistency in application. In addition, when a single review panel is responsible for overseeing the whole-spectrum review of product safety, gaps in regulatory oversight are less likely. A whole-organism focus brings all risks posed by a GMO within the responsibility of the review team. Such an umbrella approach also encourages intra- and inter-agency communication and cooperation because the team responsible for review

of a transgenic organism must consult whomever is most knowledgeable regarding each potential risk to ensure all safety criteria are met, regardless of the regulatory group to which those experts belong. With experience, the regulatory agency can develop a standardized set of safety tests and requirements. The goal becomes cooperative assessment of overall risk and safety. In addition, agency management ultimately receives a single, complete record and analysis for each new transgenic organism, allowing improved management oversight, tracking, and control. Thus, within the agency organizational structure, a whole-organism approach offers both improved horizontal interaction and improved vertical oversight.

To accomplish this shift toward comprehensive risk review, the presumption of safety in the Coordinated Framework must be revised, as must the corresponding focus on substantial equivalence review. The Coordinated Framework's focus on agency cooperation would remain unchanged, as would the emphasis on efficient and consistent regulation. Existing regulations and guidance to industry may require some change, especially with regard to the requests for product information from GMO developers, but existing statutes would not require amendment to allow for this cooperation. It is the Coordinated Framework, not the FDCA and other statutes, that adopts the policy of limited risk review.

### *3. Change Is Both Necessary and Cost Effective*

Critics of this proposal might point to the lack of any serious tragedies involving GM products over the past twenty years to demonstrate the effectiveness of the Coordinated Framework thus far. In response, although it is true that few people have been shown to have died from GM exposure, basing regulatory decisions on reaction to catastrophe is an irresponsible and ultimately costly approach to the protection of public welfare. Certainly the thalidomide incident, the experience with the escape of penned fish, the StarLink corn fiasco, and the recent USDA Inspector General criticism of APHIS's oversight of GM crop field tests all demonstrate the importance of regulatory oversight, and the massive potential costs of regulatory failure to identify and address the risks of GM products.

Critics might also decry the costs of increased regulation and the difficulty of expanding review of potential risks in light of scientific uncertainty. While it is true that the agencies can only scrutinize proposed new GM products to the extent that current analytical tools allow, a broader scope of review will identify a fuller spectrum of potential threats at the earliest possible stage. The cost to recall and remedy a GM incident is likely to be vastly higher than the cost of a broad initial scientific review. The costs of this broader scope of review

will be mitigated by the growth in institutional knowledge and experience, and the sharing of analyses between oversight agencies and units. The Coordinated Framework was created to encourage agency cooperation, and by reducing the stovepipe approach to risk analysis, the agencies will have a much greater incentive to share information and analyses. This administrative symbiosis will also conveniently reduce regulatory expenditures.

### *B. Specific Proposals for Statutory and Regulatory Changes*

The optimal revision to the biotechnology regulatory process would include passage of tactical legislative amendments to provide clear and direct statutory authority to regulate GM products and their derivatives based on both known and potential direct and environmental harms. The statutory definitions of foods, drugs, additives, and adulteration, upon which so much of GM product regulation relies, could be revised to clarify exactly how wide the FDA's authority reaches. This would eliminate the need to twist and stretch aged statutory definitions to cover applications not considered at the time of the FDCA's enactment. In addition, the creation of an FDA unit to specifically oversee all forms of GM products would address the structural division within the agency based on the crumbling distinction between foods and drugs. These changes would help to ensure that adequate review of proposed GM products is conducted before those products enter the market.

#### *1. Establish an Office of Transgenic Products*

The FDA has established separate levels of review and separate regulatory units for foods and drugs. As genetic engineering becomes more and more innovative, this distinction becomes ever more difficult to draw for individual GM products.[439] In addition, a single GMO might produce products intended for any combination of food, drug or industrial uses. The passage of legislation in 2002 to establish the Office of Combination Products within the FDA provides a very informative model of legislative and regulatory change to create a modern, efficient, and capable new regulatory mechanism within the FDA.[440] By following this example and establishing a new FDA unit charged with shepherding and overseeing the regulatory assessment and approval of every transgenic organism, the FDA would transcend its current system of

439. *See supra* note 252 and surrounding discussion.

440. *See* Medical Device User Fee and Modernization Act of 2002, Pub. L. No. 250, 116 Stat. 1588 (enabling the creation of the Office of Combination Products); FDA, Overview of the Office of Combination Products, *supra* note 5 (discussing the purposes and benefits of the creation of this new office within the FDA).

segmented review and truly become the primary regulator of transgenic organisms.

An Office of Transgenic Products would allow the FDA to move away from excessive reliance on the food and drug distinction, allowing all of the products of a transgenic organism to be considered by a single regulatory unit. This office would manage efforts to consult with other government agencies with expertise in a given area, producing the benefits of increased efficiency, economy, and quality of analysis. Like the Office of Combination Products, the proposed Office of Transgenic Products must also be enabled and encouraged to promulgate regulations and issue guidance documents to set agency policy and instruct industry regarding the steps for seeking and receiving approval of these products. Although the basic authority for these regulations already rests in the FDCA, restructuring biotechnology regulation within FDA presents an opportunity to address the gaps in statutory authority in all of the agencies regulating biotechnology.[441] Like combination products, transgenic products raise concerns about the consistency, predictability, and transparency of the regulatory process, and of which regulatory entity is responsible for each aspect of product review. Establishing a consistent regulatory regime under the leadership of a single regulatory entity promotes the fundamental goals of the Coordinated Framework to improve agency cooperation and efficiency. Although there is some intrusion on the Coordinated Framework's assumptions that existing laws and processes are sufficient, the choice to modernize the FDA, in light of modern regulatory realities and needs, better achieves the larger purposes of the Coordinated Framework and creates a more effective regulatory body.

### *2. Change Is in the Best Interest of Industry and the Public*

Proponents of deregulation and critics of the excessive reach of the administrative state might object to any expansion in statutory authority. However, as the transgenic salmon example illustrates, there is a point where the failures of existing legislation to clarify expectations and standards and authorize agency action begin to harm the efficient operation of industry more than would additional regulation.[442] Although regulatory standards foreclose some opportunities for industry creativity, they provide a mechanism for predictable, efficient, and economical regulatory review. The need for additional regulatory authority is founded in a primary government function—the protection of public welfare. This regulation is not intended to substitute government decision

441. *See* Mandel, *supra* note 187 (discussing the gaps in regulatory authority over GM products).

442. *See supra* note 355 and surrounding discussion.

making for industry preferences in the transaction of commerce. The impact on trade and innovation are intended to be no greater than necessary to prevent public harm. Thus, amendments to existing legislative authority regarding transgenics should not raise the ire of free market proponents, particularly if industry entities are given a voice in the process. Responsible biotechnology companies also want to prevent serious failures, and should be supportive of prudent government intervention. A major incident could result in significant setbacks to industry, and an excessive regulatory response in reaction to public outrage. This could ultimately prove much more costly to the industry than targeted increases in regulatory scrutiny today.[443] In addition, the ability of consumer organizations to participate in the process should imcrease public confidence in the GM regulatory process, and ultimately in the products of genetic engineering.

### *C. Post-Approval Testing to Address Persistent Uncertainty*

The Coordinated Framework came into being because of the uncertainty inherent to the genetic engineering field. Because novel transgenics have no track record upon which to rely, and because their actions and interactions are not fully predictable at the time they are created, the risks they present are very uncertain. The more transgenics diverge from conventional products, the less we can rely on analog comparisons to estimate risk potential. In 1986, the government developed the Coordinated Framework to make policy decisions regarding risk assessment. While the framework has proven too limited in its estimation of GM risks, there is still no guaranteed method for divining the true risks of an individual GMO. However, a simple and effective option for addressing the uncertainty that persists in GMO risk assessment is the implementation of a consistent post-approval assessment process.[444]

Currently, once a GM product is approved by the FDA for commercial marketing, the agency no longer considers that product unless a challenge is made regarding the safety of the product. This places a good deal of the regulatory burden on external entities such as consumer and environmental groups, scientists, academics, and industry actors themselves. To return more of this burden to the regulator, the FDA's approval process should be supplemented with a new process for periodic post-approval risk review. Optimally, this would be accompanied

443. *See supra* note 383 (discussing the StarLink corn incident).

444. Although termed a post-approval review process, to be most effective, the process would include review of all GM products, whether ultimately subject to FDA approval or not. The reach of the regulatory review depends on, and corresponds to, the extent of the statutory authority underlying the review process.

by both new statutory authority to mandate industry participation and compliance with this post-approval review process, and generation of supporting FDA regulations to establish the specific processes and parameters for the review. However, the FDA already has the authority to conduct post-approval reviews through its authority to remove a tainted or defective food or drug product from the market.[445] Based on this authority, the FDA could institute a post-approval review process immediately.

A new post-approval review process would promote early identification and intervention for unpredicted risks. This would reduce the ultimate costs of product recall or other corrective measures. The periodic review process would also inspire public and international confidence in GM products and in the U.S. biotechnology regulatory process. The ultimate parameters for such a process depend on a number of variables, including the availability and breadth of legislative change, limitations on agency resources, and results of data review to identify the best methods and subjects of post-approval scrutiny.

### *D. The Benefits of Change*

Implementing the outlined revisions in regulatory attitude, structure, and statutory authority will accrue broad benefits at a conservative cost to the regulatory agencies involved. The biotechnology industry will also benefit from the predictability and consistency offered by the new regulatory structure. The increased consumer confidences likely to be inspired both domestically and abroad would have a positive impact on GMO markets. The proposed revisions to the Coordinated Framework will improve clarity for industry and regulatory predictability, thereby promoting industry planning. Regulatory paralysis, such as that currently experienced by the FDA in determining how to regulate GM animals intended for food use, leads to both actual and opportunity costs for product developers. Inaction also harms the perception of the agency as either competent to regulate the industry or as a leader in the bioengineering product development arena.

The United States has been heavily criticized for its approach to GMO safety by both domestic and international groups. Bans on GM products have been enacted by initiative in some states, while several states are moving forward with legislation to prohibit such product bans.[446] Internationally, an approach closer to the precautionary principle has been widely adopted.[447] The United States is broadly perceived as

445. See *supra* note 161 and accompanying text (discussing product adulteration).

446. *See, e.g.*, *supra* note 243.

447. *See, e.g.*, Applegate, *supra* note 185 (considering the implications of the U.S. approach to GM risk assessment on industry and consumers); Marden, *supra* note 211 (discussing the

pushing unaffordable and unsafe GM food crops on developing nations.[448] A broader and more considered approach to GM risk assessment will address some of these fears, improve the perception of the United States, and at the same time maintain an approach to safety that is appropriate to the identifiable risks presented by a GMO. Increased consumer confidence should result in the opening of new markets to U.S. GM products and offset, to some degree, any increased cost due to broader and continuing regulatory scrutiny.

Ultimately, the proposed changes should provide a net benefit to the industry, and will definitely improve the effectiveness of the FDA and the other agencies responsible for biotechnology regulation.

## CONCLUSION

The goals of food and drug regulation—to protect human health from contaminated food or unsafe or ineffective drugs—are as vital today as they were a hundred years ago. However, the distinction between foods and drugs is no longer as clear as it once was, and this blurring will increase as transgenic applications become more innovative. Biotechnology has allowed man to develop combinations of living organisms that would never occur in the natural world. To address the evolving needs of this burgeoning field, the regulatory approach to novel transgenic products must be modified to provide a consistent and rigorous exploration of the possible risks presented by unprecedented organisms, despite persistent uncertainty regarding the nature and extent of these risks.

It is time to modernize the Coordinated Framework to truly coordinate the regulatory approach to novel transgenic organisms, across each product group, and across all of the relevant federal agencies. While agency guidance and existing laws can be further stretched to cover the emerging implications of transgenic technologies, additional legislation is necessary to cover gaps in statutory authority. No GM product, whether it be the whole organism or a derivative product, should enter the marketplace without regulatory scrutiny merely because the developer's intended use of the product is not for a purpose that fits within a century-old statutory definition. Similarly, no recognized environmental risk should remain unaddressed simply because a direct threat to human health or safety has not been sufficiently proven. A corollary to judicial deference to regulatory decision making is the need for clear agency guidance and standards.

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divergence between U.S. and European attitudes regarding the regulation of GM food products).

448. *See* Applegate, *supra* note 185; Leahy, *supra* note 244.

The biotechnology field will continue to expand rapidly as new GM options for crops, livestock, aquaculture, and medicine are developed over the coming years. Instead of waiting for a crisis to incite public opprobrium and spur legislative change, now is the time for federal agencies and Congress to demonstrate informed, creative, and inspired leadership in this emerging field.