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Item Type	Article
Authors	Lawrence, Sheryl
Publisher	UC Berkeley School of Law
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Download date	2026-09-11 13:22:12
Link to Item	http://hdl.handle.net/20.500.12424/175696

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

Sheryl Lawrence*

The Federal Food, Drug, and Cosmetics Act (FDCA) and the Coordinated Framework for the Regulation of Biotechnology are the primary federal tools for oversight of the products of genetic modification. Since their enactment, tremendous advancements in biotechnology have resulted in the creation of novel transgenic organisms, significantly unlike any pre-existing life form. The innovative nature of these transgenic products challenges fundamental assumptions of the FDCA and the Coordinated Framework. The first of these key assumptions is that the categories of “foods” and “drugs” are cleanly separable, and thus can be regulated through entirely different pathways. The FDCA and the Coordinated Framework also assume that genetically modified products do not pose inherent risks of environmental harm requiring regulatory oversight. On this basis, the United States has established a bifurcated system for the regulation of foods and drugs, in which drugs are subjected to much more rigorous scrutiny than food or industrial products. However, basing risk assessment for a novel transgenic organism on this classification places far too much weight on a distinction that is oblivious to the innate features of the transgenic product that present potential risk. Many transgenic organisms will present multiple usage possibilities, whether food, drug, or industrial,

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* Sheryl Lawrence, University of California, Berkeley, Boalt Hall School of Law, J.D., 2006. This paper was awarded the Ellis J. Harmon Environmental Law Writing Award and the Alvin and Sadie Landis prize for government law writing in 2006, by panels composed of Boalt’s environmental law faculty and practitioners. The author thanks Professor Holly Doremus for her inspiration, encouragement, and guidance in the writing of this paper. She is a star.

creating a strong potential for duplicative regulatory efforts, and for widespread unapproved uses of a product once it becomes commercially available. This focus on classification as a prerequisite for regulatory review by the Food and Drug Administration (FDA) also leaves the door open for creatures and products intended for industrial use, or as pets, to enter the marketplace without regulatory scrutiny. In addition, experience with transgenic organisms demonstrates the inadequacy of containment measures for both genetically modified plants and animals, highlighting real risks to ecology, to native species, and to other life forms posed by the unintended introduction of novel creatures into the wild. Twenty years of regulation has shown that the Coordinated Framework's regulatory structure is too inflexible, and the existing laws are too weak, to adequately address the challenges of biotechnology regulation today. To address faults in the existing regulatory structure, this Comment considers the FDA's creation of the Office of Combination Products to coordinate the regulation of interrelated classes of conventional medical products as a model for the development of a similar office overseeing the growth and marketing of genetically modified organisms and their derivative products. In addition, this Comment proposes amendments to the FDCA and the Coordinated Framework that identify and address the previously unforeseen risks presented by evolving advances in genetic engineering. Only by casting off the blinders of the Coordinated Framework and allowing federal regulators to seek out and consider the entirety of the risk potential of each novel transgenic organism can there be real confidence in the FDA's ability to broadly protect public health and safety in this amazing technological arena.

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INTRODUCTION

One hundred years have passed since the passage of the Pure Food and Drug Act of 1906,¹ the landmark law instituting federal regulation of foods and drugs in the United States and the precursor to the current Federal Food, Drug, and Cosmetics Act (FDCA).² Twenty years ago, the federal government adopted the Coordinated Framework for the Regulation of Biotechnology to encourage cooperation between the various federal agencies responsible for biotechnology regulation.³ Today, the FDCA and the Coordinated Framework are two of the most important tools used for U.S. government oversight and approval of the products of genetic modification. Under these regulatory mechanisms, remarkable advancements in genetic engineering have been achieved in recent years, leading to the creation of novel transgenic organisms and their derivative products.

However, the innovative nature of the transgenic product challenges fundamental assumptions of the FDCA and the Coordinated Framework, calling into question the structure and processes of the current regulatory system. The Coordinated Framework embraces the idea that the existing statutory authority embodied in the century-old FDCA is adequate for biotechnology regulation. Twenty years of experience have shown that the existing framework is too inflexible and existing laws too weak to adequately address modern regulatory needs, much less the more complex challenges on the horizon.

The Coordinated Framework also presumes that neither the processes used to produce genetically modified products, nor those products of genetic engineering that appear to duplicate traditionally created products, pose any new risk. On this basis, the existing statutory and administrative structure is deemed adequate for the regulation of the bioengineering processes and results. This Comment argues that even if this conclusion is true for bioengineering processes—an assertion at the heart of much academic debate⁴—the genetically modified organisms and their derivative products, themselves, may present new risks. The combination of novel genetic material into existing gene strands creates a new generation of biotechnology products not envisioned at the time the Coordinated Framework was adopted, nor at the turn of the twentieth century when the food and drug distinction was codified.

1. Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906).

2. Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended at 21 U.S.C. §§ 301–399 (2006)) [hereinafter FDCA].

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

4. See, e.g., Douglas A. Kysar, *Preferences for Processes: The Process/Product Distinction and the Regulation of Consumer Choice*, 118 HARV. L. REV. 525, 557 (2004).

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This Comment challenges several of the fundamental assumptions in the regulation of genetically engineered products in the United States. This begins with the primary assumption that all “foods” and “drugs” are cleanly separable, and thus can be regulated by entirely different regulatory pathways. As early as the Pure Food and Drug Act of 1906, the United States enacted a bifurcated system for the regulation of foods and drugs in which drugs are more rigorously scrutinized than food products. Foods were considered inherently safe, based largely on the concept that foods are made of longstanding combinations of naturally occurring components that have proven to be safe and consistent over thousands of years of cultivation and consumption. In comparison, no assumption of safety was made for drugs. Drugs are scientifically derived, novel chemical mixtures that, in theory, pose a greater risk to the consumer than foods due to the uncertainty that stems from the lack of experience and understanding of the extent of the repercussions of a drug’s use. From the start, drugs were deemed to require more regulatory review. The commonality between foods and drugs is that they are both ingested by the persons or animals intended to be protected by product safety regulations.

While the food-drug distinction might have been sufficient for products available prior to the modern era, genetic engineering permits the development of organisms with novel combinations of physical and chemical expression. When a genetic engineer combines genes from extremely different organisms, and the resulting transgenic organism offers products amenable both to food and drug uses, the traditional assumptions regarding appropriate levels of scrutiny are found wanting. To base the risk assessment of such a novel transgenic organism on the classification of each derivative product as being for either food or drug use places far too much value on the food-drug distinction. The risk potential for each of the products derived from a single transgenic organism is not lessened because a product is classified as a food instead of as a drug, and a single transgenic product might have both food and drug uses. The reasoning behind traditional classifications does not fit these nontraditional products.

This Comment illustrates the limitations of the food-drug distinction by considering several transgenic animals and plants recently developed. It first analyzes the first transgenic creature approved for sale in U.S. markets, the GloFish, an aquarium fish genetically modified with a fluorescent protein found in jellyfish genes that causes the fish to glow under fluorescent light. Next, the Comment considers a newly developed transgenic pig, also modified with the jellyfish genes so the entire pig—organs, blood, and all—is green and glows, and examines how the regulation of the transgenic pig depends on whether these pigs are used for medical research, as pets, or as a breakfast meat. The consideration of

transgenic animals intended for food use continues in an examination of transgenic salmon expected to be the first such animals to receive FDA approval for human consumption. The last illustration addresses the regulatory approval process for biopharmed plants—plants that have been modified to produce animal proteins for pharmaceutical use.

Many modern and future transgenic organisms will present both food and drug usage possibilities. Under the current regulatory framework, the degree of scrutiny each different product derived from a single organism will receive is based on the intended use of that product asserted by the product developer. The developers of the fluorescent green pigs claim that they are intended solely for medical use. The salmon developers clearly intend them for food use. Plants engineered with foreign animal proteins are not claimed to be intended for food use at this time. However, regardless of the uses originally asserted by the product developers, both modified plants and modified animals, such as the glowing pig (or its cousin, the GloFish), are conceivably open to future food uses.

Neither the FDCA nor the Coordinated Framework specifically addresses the appropriate and efficient analysis and risk assessment for novel, multiple-use products. Instead, these laws require repeated evaluation of a transgenic organism by separate regulatory units, based on the current asserted-use classification of each derivative product. Such repetition is an inefficient use of limited regulatory resources. Use-based regulatory review also opens the door to inconsistent risk assessment, as well as to manipulation of the regulatory system to gain initial approval of a transgenic product under the process offering the lowest level of scrutiny by asserting a use that receives little or no regulatory oversight. Focusing on classification as either a food or drug as a prerequisite for regulatory review means that transgenic organisms intended for uses other than food or drugs, such as for industrial use or family pet use, may go entirely unregulated.

Novel transgenics also challenge the related assumption of the FDCA and Coordinated Framework that genetically modified organisms do not pose special risks of environmental harm requiring regulatory oversight. Experience with transgenic crops and fish demonstrates the inadequacy of containment measures for both of these entities, and highlights the risks to ecological systems, including to native fish species and other life forms, posed by the unintentional introduction of the novel creature into the wild. Change to both the Coordinated Framework and the FDCA is required to establish a clear regulatory path for addressing known contamination and containment risks presented by genetically modified organisms.

To redress the flaws in the FDCA and the Coordinated Framework, the responsible agencies need to interpret existing law broadly to

effectuate the purposes of the authorizing statutes. The FDCA was enacted to protect public health and safety, and the Coordinated Framework was adopted to further that goal by enhancing agency cooperation in this complex field. Promulgation of new regulations to clarify agency expectations regarding the application of the broader statutes would promote consistent evaluation of products, predictability regarding the process for industry and the public, and consistent enforcement against violators. The reliance on voluntary participation in consultation and application processes must be replaced by a consistent and standardized review process for novel transgenics. Legislative amendment may be required to fully address the excessive reliance on the food-drug distinction, and the lack of specific, positive statutory authority regarding environmental risks.

The FDA's experience in creating an Office of Combination Products in 2002⁵ provides a model for the limited expansion of authority necessary to create an Office of Transgenic Products which would prepare for and address continuing advances in genetic engineering technology. The authority for the combination product regulations rests in the FDCA,⁶ and with a tactical legislative change the FDCA can be further adjusted to ensure that the products of genetic modification also receive appropriate regulatory oversight by the FDA. Risk assessment and regulation of transgenic products must be thorough, regardless of the intended use of the product.

* * *

Part I provides a quick explanation of terminology and briefly reviews the historical development of the food and drug laws in the United States that are now applied to the majority of the products of genetic modification technology. This Part will track the divergence in the regulatory presumptions regarding the safety of food and drugs in U.S. law.

Part II introduces the Coordinated Framework and the roles of the three federal agencies with primary involvement in the regulation of genetic modification under the Coordinated Framework: the FDA, the U.S. Department of Agriculture, and the Environmental Protection Agency.

Part III explores the implications of applying longstanding statutory definitions to emerging genetic engineering technology. This Part also considers the recent addition of the Office of Combination Products to

5. See Food & Drug Admin. (FDA), Overview of the Office of Combination Products, <http://www.fda.gov/oc/combination/overview.html> (last visited Jan. 26, 2007).

6. See Federal Food, Drug, and Cosmetic Act of 1938 § 503(g), 21 U.S.C. 353(g) (2006).

the FDA and compares the previous regulatory structure for combination products to the current regulatory structure for bioengineered products.

Part IV scrutinizes the federal regulatory experience since the implementation of the Coordinated Framework, identifying and exploring the weaknesses in the framework's assumptions revealed by the application of this regulatory structure to novel transgenic organisms. This Part also discusses the local, state, and international response to the Coordinated Framework.

Part V analyzes the special problems presented by three transgenic animals currently in existence: the GloFish, the Green Fluorescent Protein Pig, and the genetically modified Atlantic salmon. This Part also analyzes issues related to biopharming—the development and cultivation of transgenic crops or other plants to genetically express pharmaceutical or industrial chemicals foreign to the traditional plant. In all of these cases, genes from an entirely different kingdom (animal or plant), or phylum (animal subdivisions) or division (plant subdivisions), may be inserted to create a novel transgenic result. The regulatory implications of such genetic creativity are explored through each of these illustrations.

Part VI will propose and analyze suggestions for the improvement of the Coordinated Framework and the FDCA. The goal is to improve the ability of the relevant agencies to regulate effectively both under current statutory authority and with tactical legislative change.

Part VII concludes that the continued regulation of biotechnology under the Coordinated Framework and the FDCA is viable only if the FDA modifies its underlying assumptions that foods and drugs are distinct products, posing different risks and requiring separate examination. The FDA must also look beyond the idea that the risks of a novel transgenic organism are adequately identified by comparing the new organism to traditional analogs, especially as such analogs become more and more genetically different from the multiple gene source organisms of the future.

Although changing an institutional mindset is a tremendous challenge for any organization, the FDA and its related agencies have the knowledge, experience, and ability to effectively apply rigorous scrutiny to innovative transgenic organisms. Promoting broad agency authority will allow each of the agencies involved in the regulation to interact in a truly cooperative framework and thus to better protect the American people from any unexpected risks from the genetic modification of foods, drugs, and industrial products.

I. GENETIC MODIFICATION PROCESSES AND TERMINOLOGY

The ability to combine the genes of two life forms, to create an original organism with fewer weaknesses or greater strengths than its

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progenitors, is tremendously powerful. Genetic manipulation may confer on the new organism the capacity to surpass competitors, to defeat enemies, or to resist environmental pressures. Although farmers, ranchers, and even the creatures themselves have used selective breeding and culling to influence the genes of future generations for centuries,⁷ genetic engineering is a recent advancement that far surpasses these techniques and has amazing potential for expansion in future application. Genetic engineering employs scientific and technological intervention to target specific genes for recombination. Crops that resist frost, and fish that grow bigger, healthier, and faster than previous varieties are simple examples of the accomplishments of the modern genetic engineer.

Genetic engineering manipulates the deoxyribonucleic acid (DNA) in selected cells to make those cells exhibit desired traits.⁸ Unlike traditional breeding, which employs the random or uncontrolled hybridization of the parent cells, the genetic engineer chooses the specific segments of one or more DNA strands to be combined to create an original genetic sequence. Through various recombinant DNA methods,⁹

7. Charles Darwin documented the genetic selection processes innate in animal breeding choices in *ON THE ORIGIN OF SPECIES*, published in 1859. At about the same time, Gregor Mendel experimented with human manipulation of plant genes through hybridization as documented in his paper *Experiments on Plant Hybridization* published in 1866 in *PROCEEDINGS OF THE NATURAL HISTORY SOCIETY OF BRUNN*.

8. See NAT'L RESEARCH COUNCIL, *SAFETY OF GENETICALLY ENGINEERED FOODS: APPROACHES TO ASSESSING UNINTENDED HEALTH EFFECTS*, REPORT IN BRIEF 1 (2004), available at http://books.nap.edu/html/ge_foods/ge-foods-report-brief.pdf.

Nontargeted methods of genetic manipulation involve either random or uncontrolled mass recombination of genes. These methods range in their utilization of technology and include: (1) simple selection, in which plants with desired traits are selected for continued propagation; (2) crossing, in which pollen is brushed from one plant onto a sexually compatible plant to produce a hybrid with genes from both parents; (3) embryo rescue, in which a naturally cross-pollinated plant is placed in a tissue culture environment to enable its full development; and (4) mutagen breeding, in which plants, seeds, or cells are exposed to mutagenic agents such as ionizing radiation or chemicals to induce random change in the DNA sequence. The new plants are assessed for valuable traits and culled.

Among the current technological methods for achieving targeted (discrete) genetic alteration are: (1) use of microbial vectors, which take advantage of a microbe's ability to transfer and stably integrate segments of DNA into a plant so that the plant then expresses those traits; and (2) electroporation, through which plant cells growing in culture are stripped of their protective walls, then DNA is supplied to the medium and electric shock is used to destabilize the cell membrane to allow DNA to enter. As the field of genetic engineering advances and the weaknesses in existing technologies are resolved, new and more effective methods of genetic designation and combination will arise.

9. Recombinant DNA is the artificial DNA sequence resulting from the combining of two other DNA sequences in a vector, such as a plasmid or a bacteriophage. See *id.* See generally YVONNE CRIPPS, *CONTROLLING TECHNOLOGY: GENETIC ENGINEERING AND THE LAW* 6-7, 150 (1980); Wikipedia, *Recombinant DNA*, http://en.wikipedia.org/wiki/Recombinant_DNA (April 9, 2007). Plasmids are (typically) circular double-stranded DNA molecules that are separate from the chromosomal DNA. They usually occur in bacteria, which lack nuclei and other complex cell structures. Plasmids also sometimes occur in eukaryotic organisms, such as animals, plants, and fungi, which are usually multicellular and have complex cells in which the

the genetic engineer can achieve genetic transformation, ultimately producing a tailor-made, genetically modified organism.¹⁰

Genetic engineering even allows the DNA from different species or kingdoms to be joined. Inserting the hybrid DNA into a host cell such as a bacterium, and fusing the cut strands results in an entirely new transgenic DNA strand in the host cell.¹¹ The FDA has recognized that through biotechnology “essentially any trait whose gene has been identified can be introduced into virtually any plant.”¹² Such novel genetic manipulation transcends the possibilities of breeding-based hybridization and creates organisms that would never have existed without man’s intervention. The novelty of these transgenic organisms creates uncertainty regarding the new or different risks these creatures, and any product derived from them, might pose to man and the environment.

Genetic engineering is a recent advance in the bigger biotechnology field, and it is understandable that science, law, and society all have much to understand and decide with regard to this process and its resulting products. The first production of recombinant DNA molecules, using restriction enzymes, occurred in the early 1970s.¹³ The first patent on recombinant DNA technology was granted in 1980 to Herbert Boyer of the University of California, San Francisco, and Stanley Cohen of Stanford University.¹⁴ Since then, genetic science and technology have expanded exponentially.

As the biotechnology industry has grown, and the existence and application of gene-based processes have expanded, a number of terms have developed to address this emerging field. As used in this Comment, genetic modification, genetic engineering, and bioengineering all refer to the targeted manipulation of DNA in specific cells. Each of these terms is descriptive and has been used by industry, the media, academics, and federal regulatory and oversight agencies. The FDA has used the terms “bioengineered” and “genetically modified” (GM) to describe both cells

genetic material is organized into membrane-bound nuclei. A bacteriophage is a virus that infects bacteria.

10. See NAT’L RESEARCH COUNCIL, *supra* note 8.

11. See Human Genome Project, 1972 First Recombinant DNA, <http://www.genome.gov/Pages/Education/Kit/main.cfm?pageid=6> (last visited Jan. 13, 2007).

12. Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. 22,984, 22,986 (May 29, 1992).

13. See Rebecca M. Bratspies, *Consuming (F)ears of Corn: Public Health and Biopharming*, 30 AM. J.L. & MED. 371, 377–78 (2004); see also Stanley N. Cohen et al., *Construction of Biologically Functional Bacterial Plasmids In Vitro*, 70 PROC. NAT’L ACAD. SCI. U.S. 3240–44 (1973).

14. See Sally Smith Hughes, *Making Dollars Out of DNA: The First Major Patent in Biotechnology and the Commercialization of Molecular Biology, 1974–1980*, 92 ISIS 541–75 (2001).

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and foods that are genetically modified.¹⁵ In Europe, bioengineered foods are predominantly referred to as “genetically modified organisms” (GMOs).¹⁶ “Transgenic” refers to organisms, and their resulting products, which have been engineered to contain the genetic material from more than one variety of life form. Finally, the term “biotechnology” is used to refer to the field of genetic manipulation, as it is commonly used in public discourse,¹⁷ although discrete genetic modification is in fact just one segment of the greater field of biotechnology.

II. A BRIEF HISTORY OF FOOD AND DRUG REGULATION

The statutory structure for the separate regulation of foods and drugs is strongly rooted in history, which frequently demonstrates reactionary government response to highly publicized tragedies involving ingestible products, or to public disclosure of widespread fraud as the impetus for trade restrictions. This Comment explores food and drug regulation beginning with early custom, common law, and legislative efforts, followed by an introduction to the current regulatory structure under the FDCA and the Coordinated Framework for Regulation of Biotechnology. This history illustrates how the problem of establishing regulatory standards despite uncertain or unknown risk faced in the genetic engineering arena today is just the latest dilemma in Congress’ longstanding effort to balance market freedom with regulatory oversight.

A. *Early Development of Food and Drug Regulation*

Food and drug laws in the United States are rooted in English common law, and arose from concerns regarding both public safety and fraud prevention.¹⁸ The history of the regulation of foods differs from that of drugs. While early food regulation included a number of incremental legislative acts to create size and safety standards to facilitate trade, the control of medicinal products was left largely to the custom of the

15. See, e.g., Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,984; Draft Guidance for Industry: Drugs, Biologics, and Medical Devices Derived From Bioengineered Plants for Use in Humans and Animals, 67 Fed. Reg. 57,828 (Sept. 12, 2002); Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use, 69 Fed. Reg. 68,381 (Nov. 24, 2004); FDA, FDA Talk Paper: FDA Proposes Draft Guidance for Industry for New Plant Varieties Intended for Food Use (Nov. 19, 2004), <http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01327.html>.

16. Margaret Gilhooley, *Reexamining the Labeling for Biotechnology in Foods: The Species Connection*, 82 NEB. L. REV. 1088, 1095 (2004).

17. See *id.* (explaining that the National Academy of Sciences uses the term “biotechnology” to refer to genetic modification in the case of animal drugs, although the term has also been used for pharmaceuticals created without genetic engineering).

18. See Wallace F. Janssen, *America’s First Food and Drug Laws*, 30 FOOD DRUG COSM. L.J. 665 (1975).

practitioners and the pursuit of damages in tort, instead of statutory control, until relatively recent years.¹⁹

During colonial days, laws to standardize food weights and measures, cask and barrel sizes, and to allow inspection and certification of food packing and sealing were enacted to protect and promote trade.²⁰ The protection of the citizenry from tainted foods was initially linked to efforts to prevent economic harm to merchants resulting from incidents of product spoilage, not from any concern about the inherent nature of the food product itself. Massachusetts required fish inspection as early as 1668, because trade had been negatively affected by the “bad making of Fish.”²¹ That same year, Massachusetts passed a food additive law banning the use of “Tortoodas Salt” due to product contamination, explaining that the salt “leaves spots upon fish, by reason of shells and trash in it.”²² In 1785, the General Court of Massachusetts passed the “Act against selling unwholesome provisions” to protect consumers against unwholesome foods.²³ This was the first comprehensive food adulteration law in the United States, and it established criminal penalties for violators.

Unlike food regulation, early protections against misbranded, ineffective, or poisonous drugs were undertaken without the benefit of enforceable regulatory statutes. Instead, common law fraud was used as early as 1630 to address the sale of a scurvy medicine of “noe worth nor value.”²⁴ In the seventeenth century, the Massachusetts and New York colonies adopted “An Act Respecting Chirurgions, Midwives and Physicians” to create a loose code of ethics for medical practitioners, but failed to establish enforcement mechanisms or specific practice requirements.²⁵ The lack of scientific knowledge regarding physiology and chemistry, combined with the popular desire to actively treat the many illnesses of the day, led both to the development of a myriad of quack medications and treatments throughout the eighteenth century and to the inability or unwillingness of legislators to enact regulations to restrict or prohibit supposed medical practitioners in their attempts to prevent and treat illness.²⁶

By the nineteenth century, consumer products increasingly were generated from centrally processed sources, and the adulteration of food

19. *See id.* at 669.

20. *See id.* at 667.

21. *Id.* at 668.

22. *Id.*

23. *Id.* at 668–69.

24. *Id.* at 669 (discussing sentencing of Nicholas Knopp by the Massachusetts Court of Assistants in 1630).

25. *See id.* at 669–70.

26. *See id.* at 669–71.

and drugs with bacteria, toxins, or other harmful agents became widespread.²⁷ Nonetheless, it was not until 1848 that the United States enacted its first federal drug law, the Import Drug Act, in response to the discovery of gross adulteration and inadequate potency of anti-malarial medication used by U.S. troops in Mexico.²⁸ In 1862, the British Parliament passed its first national food adulteration act, the “Bill for Preventing Adulteration of Articles of Food and Drink,” after a druggist’s assistant in a small English town poisoned 400 people by accidentally putting arsenic in peppermint lozenges.²⁹ Despite the experience in England, the United States did not respond with a national food law of its own for over forty years.

B. The Emergence of Modern Food and Drug Regulation

Modern food and drug regulation in the United States began with the Pure Food and Drug Act of 1906,³⁰ following sensational muckraking publications that revealed both quackery in patent medicines, and the unsanitary conditions, fraud, and corruption in the food processing industry.³¹ Prominent among these publications was a series of articles by Samuel Hopkins Adams, published in *Collier’s Weekly*, that exposed many patent medicines as simple mixtures composed mostly of alcohol.³² For example, the formula for “Peruna,” a popular remedy, was published: one-half pint of 90 percent proof spirits, 1.5 pints of water, a flavor cube,

27. See, e.g., *id.* at 665; James Harvey Young, *The Long Struggle for the 1906 Law*, FDA CONSUMER, June 1981, available at <http://vm.cfsan.fda.gov/~lrd/history2.html>; Wallace F. Janssen, *The Story of the Laws Behind the Labels*, FDA CONSUMER, June 1981, available at <http://vm.cfsan.fda.gov/~lrd/history1.html>; FDA, Milestones in U.S. Food and Drug Law History (May 1999, updated Aug. 2005), <http://www.fda.gov/opacom/backgrounders/miles.html>.

28. See Janssen, *supra* note 18, at 672.

29. Patricia I. Carter, *Federal Regulation of Pharmaceuticals in the United States and Canada*, 21 LOY. L.A. INT’L & COMP. L. REV. 215, 216 (1999).

30. Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906).

31. See Richard M. Cooper, *An Introduction to Food and Drug Law and Regulation*, in 1 FUNDAMENTALS OF LAW AND REGULATION: AN IN-DEPTH LOOK AT FOODS, VETERINARY MEDICINES, AND COSMETICS 2 (Robert P. Brady et al. eds., 1997).

32. Samuel Hopkins Adams, *The Great American Fraud*, COLLIER’S WEEKLY, Oct. 7, 1905. *Collier’s Weekly* published a series of articles by Adams, providing

[a] full explanation and exposure of patent medicine methods and the harm done to the public by this industry, founded mainly on fraud and poison. Results of the publicity given to these methods can be already seen in the steps recently taken by the National Government, some State Governments, and a few of the more reputable newspapers. The object of the series is to make the situation so familiar and thoroughly understood that there will be a speedy end to the worst aspects of the evil.

See *id.*; see also PHILIP J. HILTS, PROTECTING AMERICA’S HEALTH: THE FDA, BUSINESS, AND ONE HUNDRED YEARS OF REGULATION 48 (2003) (explaining that Peruna was called a “catarrh” and was used for colds, congestion, tuberculosis, mumps, and “female problems”); Richard Curtis Litman & Donald Saunders Litman, *Protection of the American Consumer: The Muckrakers and the Enactment of the First Federal Food and Drug Law in the United States*, 36 FOOD DRUG COSM. L.J. 647, 651–53, 662–64 (1981).

a little burned sugar for color.³³ Another such curative, “Liquozone” was composed of 99 percent water and 1 percent sulfuric acid (for medicinal taste), and was used for ailments ranging from asthma to dandruff to dental pain.³⁴ Adams explained that the harm of these concoctions was that those who used them believed that they were being treated and consequently did not visit a doctor until it was too late.³⁵

In addition to these articles on the fraud of patent medicines, other muckrakers addressed the increasing problems in the food processing industries. Upton Sinclair’s *The Jungle*, published in 1906, highlighted the disgusting conditions in U.S. meatpacking facilities.³⁶ Such publications raised public support for increased government regulation.

In 1906, Congress enacted the Pure Food and Drug Act, a landmark in Progressive-era legislation.³⁷ Dr. Harvey W. Wiley, recognized as the “pioneer consumer advocate,” led the fight for a federal food and drug regulatory act.³⁸ The Pure Food and Drug Act passed with overwhelming support in Congress, despite opposition from food and drug manufacturers concerned that it would curtail business.³⁹ Although this early law did not require government review of food or drugs prior to marketing, it did specify conditions under which these types of products would be considered adulterated or misbranded. The Act required all drugs recognized in the United States Pharmacopoeia or National Formulary to meet national testing standards unless clearly stated on the packaging.⁴⁰ Listed drugs not meeting national standards had to state and meet their own standards for strength, quality, and purity. For a small subset of drugs considered especially dangerous, the Act required the

33. Adams, *supra* note 32, at 36.

34. *Id.* at 20–21.

35. See HILTS, *supra* note 32, at 48.

36. UPTON SINCLAIR, *THE JUNGLE* (Bantam Classics 1983) (1906). Sinclair’s assertions were confirmed in the Neill-Reynolds report, commissioned by President Franklin Roosevelt in 1906. The President was suspicious of Sinclair’s socialist ideology, so he sent men he trusted, Labor Commissioner Neill and social worker Reynolds, to Chicago to verify Sinclair’s account through surprise visits to the meatpackers. Despite the fact that the meatpackers were warned of the plan before the “secret” inspections took place, allowing them to work three shifts a day to clean the factories before the President’s inspectors arrived, Neill and Reynolds were still revolted by the conditions at the factories and the lack of concern by managers. Following their report, President Roosevelt became a supporter of regulation of the meatpacking industry. See HILTS, *supra* note 32, at 51–53. The Federal Meat Inspection Act, Pub. L. No. 59-382, 34 Stat. 674 (1906) (codified at 21 U.S.C. §§ 601–691 (2006)) was passed on the same day as the Pure Food and Drug Act in 1906. See *id.*

37. See Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768; see also FDA, A Guide to Resources on the History of the Food and Drug Administration (2002), <http://www.fda.gov/oc/history/resourceguide/background.html>.

38. See Harvey W. Wiley: Pioneer Consumer Activist, FDA CONSUMER, Jan.–Feb. 2006, http://www.fda.gov/fdac/features/2006/106_wiley.html; see also Janssen, *supra* note 18.

39. See Carter, *supra* note 29, at 217.

40. See *id.*; Pure Food and Drug Act of 1906 § 7.

drug's label to state the ingredients and quantities contained in the package.⁴¹

The Pure Food and Drug Act had significant defects and omissions. Although the Act established some protections from fraudulent medicines, it did not adequately assure safe and effective products, authorize bans on unsafe drugs, or require drug labels to identify contents.⁴² The Act also exempted therapeutic assertions from false and misleading statement requirements, allowing purported medical practitioners to make extravagant and unsupported claims about the therapeutic benefits of their products.⁴³ In the years following 1906, several amendments to the Pure Food and Drug Act were passed to address these problems, with limited effectiveness.⁴⁴

Real improvement did not come until the sulfanilamide disaster of 1937, which focused public and political attention on the weaknesses of the United States' food and drug regulations and dramatized the need to establish drug safety before product marketing. Sulfa drugs were used throughout the United States during the 1930s, and one drug manufacturer decided to produce a more palatable, liquid version of sulfa with a sweet, raspberry taste. This was achieved by adding a poisonous chemical, diethylene glycol, regularly used in antifreeze. The Elixir of Sulfanilamide killed 107 people in the United States including many children.⁴⁵ No clinical tests were required or performed prior to the marketing of this new product to the general public.⁴⁶ Popular outrage following the disaster expedited the enactment of a revised food and drug law that had been recommended by the FDA in 1933, but had been stalled for five years in legislative debate.⁴⁷ Spurred into action, Congress passed the Federal Food, Drug and Cosmetic Act of 1938.⁴⁸

41. Pure Food and Drug Act of 1906 § 8; *see also* Carter, *supra* note 29, at 217.

42. *See* Carter, *supra* note 29, at 217–18. The Pure Food and Drug Act also did not cover cosmetics. The regulation of cosmetics is outside of the scope of this Comment, and so will be omitted from the discussion of food and drug regulations.

43. *See id.* at 218; *see also* *United States v. Johnson*, 221 U.S. 488 (1911) (holding that the Pure Food and Drug Act did not prohibit false therapeutic claims but only false and misleading statements about the ingredients or identity of a drug).

44. *See* Carter, *supra* note 29, at 218. For example, the Sherley Amendment, passed by Congress in 1912 in response to the holding in *United States v. Johnson*, 221 U.S. 488, prohibited false or misleading therapeutic claims. Sherley Amendment, Pub. L. No. 62-301, 37 Stat. 416 (1912) (amended 1913). However, the amendment shifted the burden of proof to the government by adding the requirement that the claim be fraudulent, effectively nullifying the enforceability of legislation. *See* Carter, *supra* note 29, at 218.

45. *See* FDA, Milestones, *supra* note 27.

46. *See* Carter, *supra* note 29, at 218.

47. *See* FDA, Milestones, *supra* note 27; HILTS, *supra* note 32, at 51–53.

48. Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified at 21 U.S.C. §§ 301–399 (2006)).

C. Developments in the Federal Food, Drug, and Cosmetic Act

The Federal Food, Drug and Cosmetic Act (FDCA) greatly expanded the FDA's authority, permitting the agency to require drug manufacturers to prove new drugs to be safe before marketing; to regulate medical devices and cosmetics; and to establish standards for the identity, quality, and fill of food containers.⁴⁹ The FDCA authorized the FDA to set safe tolerances for unavoidable poisonous substances in foods and to conduct inspections of medical and food processing facilities.⁵⁰ The FDCA also added the remedy of court injunction to the existing Pure Food and Drug Act penalties of seizure and prosecution, allowing the FDA to stop a faulty product from reaching the market before anyone is harmed.⁵¹ Since its initiation, the FDCA has been amended several times to expand the products regulated and to create new regulatory procedures.⁵²

The modern era of drug regulation also originated from the catastrophic failure of the drug thalidomide, which prompted major new legislation to strengthen and extend the FDCA's drug approval requirements. Thalidomide was a sleeping pill developed and widely used in Europe in the 1950s and 1960s.⁵³ In the United States, a researcher performing an investigative study of thalidomide discovered that severe teratogenic effects, such as flipper-like hands or feet in the fetus, could result if pregnant women took the drug during the first trimester.⁵⁴ The study showed that more than a thousand children born in Europe suffered severe congenital malformations due to the mothers' ingestion of thalidomide during pregnancy.⁵⁵ Fortunately, the FDA had not approved thalidomide for widespread use in the United States and the drug was

49. See Cooper, *supra* note 31, at 3. The FDCA also eliminated the Sherley Amendment requirement that the government prove intent to defraud in drug misbranding cases. See *id.*; FDA, Milestones, *supra* note 27; see also *supra* note 44.

50. See FDA, Milestones, *supra* note 27.

51. See *id.*

52. Additions include a series of amendments to regulate insulin, antibiotics, drug prescriptions, medical devices, animal medicines, and dietary supplements, among others. See, e.g., Pub. L. No. 77-366, 55 Stat. 851 (1941) (insulin); Pub. L. No. 79-139, 59 Stat. 463 (1945) (penicillin); Pub. L. No. 90-16, 61 Stat. 11 (1947) (streptomycin); Durham Humphrey Act of 1951, Pub. L. No. 82-215, 65 Stat. 648 (establishing a statutory basis for the drug prescription requirement); Animal Drug Amendments of 1968, Pub. L. No. 90-399, 82 Stat. 342; Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585; Safe Medical Devices Act of 1990, Pub. L. No. 101-629, 104 Stat. 4511; Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, 108 Stat. 4325.

53. See HARVEY TEFF & COLIN MUNRO, THALIDOMIDE: THE LEGAL AFTERMATH 1 (1976).

54. See Carter, *supra* note 29, at 219-20.

55. See *id.* at 220; TEFF & MUNRO, *supra* note 53, at 4-5 (stating that several thousand children in Germany alone suffered birth defects from thalidomide).

only permitted in limited distribution.⁵⁶ Public attention to the link between thalidomide and the deformed children in Europe facilitated the passage of amendments to the FDCA that were pending at the time.⁵⁷ Congress passed the Kefauver-Harris Amendments to the FDCA in 1962, substantially broadening the powers of the FDA, especially as related to drug testing and approval.⁵⁸ This began a serious divergence in the regulatory treatment of foods and drugs, as new drug review and approval requirements became much more stringent than the controls on new food products.

Although the 1938 FDCA legislation created a framework in which pharmaceutical manufacturers were required to submit New Drug Applications (NDAs) prior to commercial development of a drug, regulatory approval of new drugs was not required under the original FDCA statute. Instead, NDA approval was automatic unless the FDA disapproved the drug within sixty days of submission of the application.⁵⁹ This deemer provision created a prompt, but not especially rigorous, mechanism for drug regulation. The 1962 FDCA amendments established the modern prior approval procedures for evaluating Investigational New Drugs (INDs) and NDAs.⁶⁰ These amendments strengthened the regulation of drug development and manufacturing by requiring drug companies to prove that each new drug is both safe and effective, through “substantial evidence,” before the FDA will approve marketing of the drug.⁶¹ Thus, the 1962 amendments made affirmative approval by the FDA mandatory to the commercial distribution of new drugs, and required the submission of empirical data supporting drug efficacy as a crucial element of the NDA process.⁶² Standards for Good Manufacturing Practices (GMP) were established, and any drug manufactured without adherence to these standards was presumed adulterated.⁶³ The FDA was also given authority over prescription drug advertising.⁶⁴ The 1962

56. See Susan Bartlett Foote & Robert J. Berlin, *Can Regulation Be as Innovative as Science and Technology? The FDA's Regulation of Combination Products*, 6 MINN. J. L. SCI. & TECH. 619, 626 (2005).

57. See TEFF & MUNRO, *supra* note 53, at 118–24.

58. See Carter, *supra* note 29, at 219–20; Public Law Drug Amendments of 1962, Pub. L. No. 781, 76 Stat. 780.

59. See Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U. J. LEGIS. & PUB. POL'Y 295, 303 (1999–2000). The 1962 amendments first established the FDA's pre-market approval responsibility for new drugs, based upon empirical demonstration of drug efficacy. See *id.*

60. Public Law Drug Amendments of 1962 § 104, Pub. L. No. 781, 76 Stat. 780 (modifying § 505(a) of the Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040), (codified at 21 U.S.C. § 355(a) (2006)).

61. *Id.*

62. See Greenberg, *supra* note 59, at 303.

63. See Public Law Drug Amendments of 1962 § 101 (modifying FDCA § 501(a), 21 U.S.C. § 351(a)).

64. See *id.* § 131 (adding subsection (n) to FDCA § 502, 21 U.S.C. § 352(n)).

amendments also extended the legal and procedural distance between the FDA's regulation of drugs and medical devices.⁶⁵

The establishment of these rigorous new drug approval requirements further emphasized the divergence between food and drug regulation under the FDCA. While a complex mechanism was established under which manufacturers must prove the safety and effectiveness of each new drug before entering the market, food safety continued to be regulated through a less rigorous set of standards and thresholds for contaminants and toxins. The FDA enacted an inspection program for food processing facilities. If handled properly, foods were still considered to be inherently safe, so no requirement for "new food" approval, demanding proof of safety like "new drugs," was established. Unlike the experience with drugs like sulfanilamide and thalidomide, there was no food-related tragedy caused by the inherent characteristics of a food product to incite the public to demand tighter controls on foods. Food-related incidents resulted from spoilage or contamination of an otherwise safe food, not from hazards inherent to the composition of the food itself.

The conceptual division between food and drugs became structural within the operation of the FDA, and also statutory as the laws for the regulation of foods and drugs diverged. Different units handle food or drug oversight, under different review standards. Both traditional and innovative ingestible products are classified as foods or drugs, and then reviewed under the indicated agency protocol. The FDCA, with its bifurcated approach, remains the primary law for the regulation of foods and drugs today, despite enormous biotechnological change resulting in significant merger in the inherent characteristics of food and drugs.⁶⁶ Novel transgenic organisms, and their derivative products, illustrate this combining of foods and drugs, and illuminate the weaknesses of the FDA's approach.

D. Introduction of the Coordinated Framework

The emergence of the biotechnology industry in the 1970s and 1980s again tested the capacity of the FDCA to protect the public from unacceptable food and drug risks. As genetic modification evolved from concept into a practical method for product development, identification of the inherent risks of bioengineered products and approval of these products for commercial marketing was primarily left to the FDA under the authority of the FDCA. However, numerous other agencies also play a role in regulating the study, manufacture, or production of the new GM

65. See Foote & Berlin, *supra* note 56, at 625–26.

66. See *id.* The specific statutory requirements of the FDCA are discussed further below.

products.⁶⁷ To address recurring industry criticism of a perceived lack of coordination in biotechnology policy between the many government institutions involved in the bioengineering field, President Ronald Reagan created a Cabinet Council Working Group to study the issue in 1984.⁶⁸ The result was the issuance of the “Coordinated Framework for the Regulation of Biotechnology” on June 26, 1986, by the President’s Office of Science and Technology Policy.⁶⁹ Although not a legislative enactment, the Coordinated Framework instituted a “comprehensive federal regulatory policy for . . . biotechnology research and products.”⁷⁰ Despite the many advances in the GM field, the twenty-year-old framework remains in effect today.

Under the Coordinated Framework, three agencies—the FDA, the USDA, and the EPA—dominate regulatory oversight of genetically engineered products in the United States.⁷¹ The FDA evaluates the safety and marketing of GMOs intended for human or animal consumption under the FDCA. The USDA, acting through its Animal and Plant Health Inspection Service (APHIS), monitors the growth of GM crops under the Plant Protection Act.⁷² Finally, the EPA regulates environmental risks posed by organisms modified to contain insecticidal properties under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)⁷³ and the Toxic Substances Control Act (TSCA).⁷⁴

The Coordinated Framework is founded in the basic assumptions that existing law is adequate to address the needs of GM product regulation and that GM products inherently present no new risks beyond those of conventional analog organisms.⁷⁵ GM products are presumed safe in the absence of physical differences from the analogous components of the progenitor organisms. This Comment explains and examines the results of the application of the Coordinated Framework over the past twenty years, culminating in a proposal for improving the transgenic regulatory process.

67. See Coordinated Framework for the Regulation of Biotechnology, 51 Fed. Reg. 23,302 (June 26, 1986) (announcing the policy of the federal agencies involved with the review of biotechnology research and products).

68. See THOMAS BERNAUER, GENES, TRADE, AND REGULATION: THE SEEDS OF CONFLICT IN FOOD BIOTECHNOLOGY 55 (2003).

69. Coordinated Framework for the Regulation of Biotechnology, 51 Fed. Reg. 23,302 (June 26, 1986). See also NAT’L RESEARCH COUNCIL, GENETICALLY MODIFIED, PEST-PROTECTED PLANTS: SCIENCE AND REGULATION 144 (2000).

70. Coordinated Framework, 51 Fed. Reg. at 23,302.

71. See MICHAEL R. TAYLOR ET AL., PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, TENDING THE FIELDS: STATE & FEDERAL ROLES IN THE OVERSIGHT OF GENETICALLY MODIFIED CROPS 15 (2004), available at <http://pewagbiotech.org/research/fields/report.pdf>.

72. 7 U.S.C. §§ 7701–7786 (2006).

73. *Id.* §§ 136–136y.

74. 15 U.S.C. §§ 2601–2692 (2006).

75. See *infra* note 184 and surrounding discussion.

III. HOW THE FOOD AND DRUG DISTINCTION IS APPLIED TO GM PRODUCTS

A. Food and Drug Definitions Under the FDCA

The Food and Drug Administration, through the FDCA, establishes separate systems of regulation for foods and drugs based on the manufacturer's intended use of the product. By fitting the products of bioengineering into the FDCA's existing regulatory categories, the FDA applies the general concepts of product approval, adulteration, and misbranding to regulate safety and effectiveness across the spectrum of GM food and drug products. However, GM products are becoming more innovative as genetic engineers combine genes from completely unrelated organisms to create novel life forms. Such combinations create organisms that express chemicals not native to conventional organisms. As GM products become more innovative, categorizing the resulting organisms and their derivative products challenges existing food and drug definitions.

In order to analyze the ability of the current regulatory structure to address the current and future needs of the bioengineering field, the definitions used under the existing statutory scheme must be considered. The ability of a regulator to review or restrict an activity often depends on whether that activity falls within statutory definitions. No matter how technologically savvy and effective its regulatory program becomes, the FDA can exert authority only over those products satisfying statutory definitions. The following subpart explains the pertinent provisions of the FDCA that limit or grant authority over the regulation of GM products, including discussion of judicial interpretations of the statutory language.

1. Food Definitions

The definitions relevant to the regulation of GM food products include the distinctions between food and feed, the requirements for food additives, and the elements of misbranding and adulteration.

a. Food and Feed Definitions

Under the FDCA, food regulation is based on the classification of a product as a "food," "animal feed," or "food additive." Food substances are not permitted to enter the marketplace if they are deemed "adulterated." For GMOs, the developer's intended use of the whole plant or animal or its derivative products directs the initial determination of whether the item qualifies as food or feed. The regulatory hurdles for those products intended for food use depend on the initial determination of whether the food has been adulterated. The FDA reviews the specific aspect of the new organism that was genetically modified to determine

whether the substance qualifies as adulterated and therefore must be restricted from the public marketplace.

i. Foods

The FDCA defines “food” as: “(1) articles used for food or drink for man or other animals; (2) chewing gum; and (3) articles used for components of any such article.”⁷⁶ Recognizing the circularity of this definition, the 7th Circuit offered the following explanation:

When the statute defines “food” as “articles used for food,” it means that the statutory definition of “food” includes articles used by people in the ordinary way most people use food—*primarily* for taste, aroma, or nutritive value. To hold . . . that articles used as food are articles used *solely* for taste, aroma, or nutritive value is unduly restrictive since some products such as coffee or prune juice are undoubtedly food but may be consumed on occasion for reasons other than taste, aroma, or nutritive value.⁷⁷

The definition of food has not changed since originally enacted in 1938, although over the years courts have interpreted this definition as applied to certain foods and related products.⁷⁸ For example, food-packaging materials themselves may be construed as “food” under the FDCA, when the contents of the packaging material could migrate into the food.⁷⁹

ii. Animal Feed

The FDCA also covers foods intended for consumption by animals. “Animal feed” is defined to include articles “intended for use for food for animals other than man and which are intended for use as a substantial source of nutrients in the diet of the animal.”⁸⁰ GM corn and other crops are especially likely to be used as animal feed, and transgenic fish are likely to enter this category soon.⁸¹

76. Federal Food, Drug, and Cosmetic Act of 1938 § 201(f), 21 U.S.C. § 321(f) (2006). The FDCA also covers the regulation of cosmetics, but this Comment is limited to discussion of foods and drugs, touching on medical device regulation. Cosmetics are not addressed.

77. *Nutrilab, Inc. v. Schweiker*, 713 F.2d 335, 338 (7th Cir. 1983) (referring to the District Court in *Nutrilab, Inc. v. Schweiker*, 547 F. Supp. 880, 883 (N.D. Ill. 1982)).

78. While FDA in theory has jurisdiction over all foods, FDA does not regulate meat and poultry products. These products are regulated primarily by the USDA. *See* Federal Meat Inspection Act, 21 U.S.C. §§ 601–695 (2006); Poultry Products Inspection Act, *id.* §§ 451–471; *see also* Martin Hahn, *Functional Foods: What Are They? How Are They Regulated? What Claims Can Be Made?*, 31 AM. J.L. & MED. 305, 307 (2005).

79. *See* *Natick Paperboard Corp. v. Weinberger*, 389 F. Supp. 794, 797–98 (D. Mass.), *aff’d*, 525 F.2d 1103 (1st Cir. 1975). This food-packaging holding could have interesting implications for GM crops, if stalks, hulls, or any other portion are used in the manufacture of packaging materials with the potential to migrate into the food product.

80. Federal Food, Drug, and Cosmetic Act of 1938 § 201(w), 21 U.S.C. § 321(w); *see also id.* § 360b (regulating animal feed containing animal drugs).

81. *See* discussion of transgenic salmon in Part V.B.3.

iii. Food Additives

Vital to the regulation of genetically modified organisms and the products derived therefrom is the definition of “food additive.” This term includes:

any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing . . . transporting, or holding [of] food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts . . . as having been adequately shown through scientific procedures . . . to be safe under the conditions of its intended use⁸²

Exceptions to this definition include pesticide chemicals and their residue, color additives, and any product otherwise determined to be a new animal drug or intended to be used as an ingredient for a dietary supplement.⁸³

iv. Misbranding

The FDA will reject a food or feed from commercial marketing if the product is determined to have been misbranded.⁸⁴ “Misbranding” includes using false or misleading labels, packaging, or containers.⁸⁵ The issue of whether genetically engineered products should be labeled to inform consumers of the GM content, and to avoid assertions of misbranding, is highly contentious and has received a great deal of academic, legislative, and public scrutiny.⁸⁶ Both misbranding and adulteration of foods are subject to criminal penalties, and a violator may be prosecuted for either or both.⁸⁷

82. FDCA § 201(s), 21 U.S.C. § 321(s) (emphasis added).

83. FDCA § 201(s), 21 U.S.C. § 321(s). Dietary supplements are generally deemed foods within the meaning of the FDCA. *See* FDCA § 201(ff), 21 U.S.C. § 321(ff). Analysis of dietary supplements is beyond the scope of this Comment.

84. FDCA § 403, 21 U.S.C. § 343.

85. *See* FDCA § 403, 21 U.S.C. § 343; *see also* 21 U.S.C. § 352 (classifying misbranded drugs and devices); *United States v. Haas*, 171 F.3d 259, 266 (5th Cir. 1999) (finding that selling drugs not approved by the FDA in United States that were filled by a pharmacist in Mexico as cost-saving alternative is misbranding); *United States v. Dino*, 919 F.2d 72, 75 (8th Cir. 1990) (holding that selling drugs without expiration dates, serial numbers, or marked lot numbers constitutes misbranding).

86. *See* Gilhooley, *supra* note 16, at 1101–05, 1108; Draft Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering, 66 Fed. Reg. 4839, 4840 (Jan. 18, 2001); DONNA U. VOGT & BRIAN A. JACKSON, CONG. RESEARCH SERV., LABELING OF GENETICALLY MODIFIED FOODS (2000), available at <http://www.ncseonline.org/NLE/CRSreports/Agriculture/ag-98.cfm>.

87. *See* Federal Food, Drug, and Cosmetic Act of 1938 §§ 301–303, 21 U.S.C. §§ 331–333 (2006) (prohibited acts and penalties); *see, e.g.*, *In re Orthopedic Bone Screw Prods. Liab. Litig.*,

v. Adulteration of Food and Feed

The FDA will deny approval of “adulterated” GM products. Food is deemed to be adulterated if it is “[p]oisonous, insanitary,” or contains “deleterious” ingredients.”⁸⁸ This includes foods or feed with an added substance that may render the food “injurious to health” or “unsafe,”⁸⁹ or that “bears or contains” a pesticidal chemical residue, food additive, or new animal drug that is deemed “unsafe.”⁹⁰ This definition includes both substances that are problematic in themselves, such as meat from a diseased animal, and conditions that may taint otherwise acceptable foods, such as weevil-infested grains.

The statutory definition of adulterated foods also includes the “[a]bsence, substitution, or addition of constituents” to a food.⁹¹ Food is adulterated under this provision if:

- (1) any valuable constituent has been in whole or in part omitted or abstracted therefrom; or
- (2) any substance has been substituted wholly or in part therefor; or
- (3) damage or inferiority has been concealed in any manner; or
- (4) any substance has been added thereto or mixed or packed therewith so as to increase its bulk or weight, or reduce its quality or strength, or make it appear better or of greater value than it is.⁹²

Thus, the removal of genes from a traditional organism used for food or feed purposes, while otherwise statutorily allowable, could result in the product being designated as adulterated if a new genetic expression replaces a traditional trait of that organism. Correspondingly, the addition or substitution of genetic material in an otherwise compliant conventional food might also be considered an adulteration.

b. *FDA Guidance on Genetically Modified Foods*

For a genetically modified food product to be approved, the FDA must determine that the modification did not result in adulteration of a “valuable constituent” of that food.⁹³ To supplement this vague standard, in 1992 the FDA developed limited guidance for industry, the “Statement of Policy: Foods Derived From New Plant Varieties,” seeking voluntary

193 F.3d 781, 786 (3d Cir. 1999) (recognizing distinct crimes of adulteration and misbranding under FDCA).

88. FDCA § 402(a), 21 U.S.C. § 342(a).

89. *Id.* “Unsafe” here refers to FDCA § 406, 21 U.S.C. § 346 (defining added substance).

90. FDCA § 402(a), 21 U.S.C. § 342(a). “Unsafe” here refers to FDCA § 408(a), 21 U.S.C. § 346a (defining pesticide chemical).

91. FDCA § 402(b), 21 U.S.C. § 342(b).

92. *Id.*

93. *Id.*

compliance with suggested review standards for new plant varieties.⁹⁴ The FDA has not promulgated any mandatory regulations to clarify implementation of the statutory language regarding food adulteration.

The FDA's 1992 Statement set testing guidelines for new plant varieties intended for food use.⁹⁵ The guidelines apply to all new plant varieties, regardless of whether the new variety was developed through traditional breeding or genetic engineering.⁹⁶ The Statement relies on plant developers to ensure the safety of their own products and identifies the types of food safety issues that developers are expected to investigate and address in their internal safety evaluation of their new plant products.⁹⁷ In addition, the FDA announced that it would presume that foods produced through recombinant DNA (rDNA) processes are "generally recognized as safe" (GRAS) under the FDCA,⁹⁸ in the absence of evidence to the contrary, and therefore are not subject to regulation as food additives.⁹⁹ Thus, the burden rests on a party challenging a genetically modified food product to rebut the presumption of safety by presenting physical evidence of a safety hazard inherent to the GM product.

The FDA's Statement on new plant varieties bases its reasoning on the concept that the only substances added to bioengineered foods are nucleic acids which in themselves are generally recognized not only as safe, but also as essential to human existence.¹⁰⁰ The FDA explained that, "Nucleic acids are present in the cells of every living organism, including every plant and animal used for food by humans or animals, and do not raise a safety concern as a component of food."¹⁰¹ However, the FDA does recognize that "the intended expression product in a food could be a protein, carbohydrate, fat or oil, or other substance that differs significantly in structure, function, or composition from substances found currently in food."¹⁰² The FDA therefore concludes that, "[s]uch substances may not be GRAS and may require regulation as a food additive."¹⁰³

94. See Statement of Policy: Foods Derived From New Plant Varieties, 57 Fed. Reg. 22,984, 22,991 (May 29, 1992).

95. *Id.* at 22,984.

96. See *id.* The recombinant DNA (rDNA) process is recognized as the most prevalent technique used in genetic engineering to create new plant varieties.

97. See Linda Bren, *Genetic Engineering: The Future of Foods?*, FDA CONSUMER, Nov.–Dec. 2003, available at http://www.fda.gov/fdac/features/2003/603_food.html.

98. The meaning of "generally recognized as safe" is provided in the Federal Food, Drug, and Cosmetic Act of 1938 § 201(s), 21 U.S.C. § 321(s) (2006).

99. See Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,989–91.

100. See *id.* at 22,990.

101. *Id.*

102. *Id.* at 22,984, 22,990.

103. *Id.*

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The FDA also announced that it would require food additive petitions to address those situations in which “safety questions exist sufficient to warrant formal pre-market review by FDA to ensure public health protection.”¹⁰⁴ Because the FDA’s own product safety review will be based on a presumption of safety, questions of food safety will likely come from extra-agency sources or derive from extra-agency research data. While the FDA recommended that food producers voluntarily consult with the agency before marketing GM foods, the agency did not mandate such consultation.¹⁰⁵ The FDA reserved the right to regulate any rDNA-developed food that it determined through ad hoc review to be unsafe in the same manner that the FDA regulates individual foods produced through conventional means that are deemed unsafe after being introduced in the marketplace.¹⁰⁶ The FDA concluded that “[u]ltimately, it is the food producer who is responsible for assuring safety.”¹⁰⁷

In 2004, after a dozen years of biotechnology regulation experience, and with an explosion of innovative transgenic products on the horizon, the FDA issued new draft guidance for industry which recognized a greater potential for risk from GM products than had previously been acknowledged.¹⁰⁸ The FDA recognized that, “[r]apid developments in genomics are resulting in dramatic changes in the way new plant varieties are developed and commercialized,” and that “[s]cientific advances are expected to accelerate over the next decade, leading to the development and commercialization of a greater number and diversity of bioengineered crops.”¹⁰⁹ The FDA also acknowledged that, “[a]s the number and diversity of field tests for bioengineered plants increase, the likelihood that cross-pollination due to pollen drift from field tests to commercial fields and commingling of seeds produced during field tests with commercial seeds or grain may also increase.”¹¹⁰ This might result in “low-level presence in the food supply of material from new plant varieties that have not been evaluated through FDA’s voluntary [biotechnology] consultation process.”¹¹¹ Despite the recognized contamination risk to conventional foods from unapproved GM products,

104. *Id.*

105. *See id.* at 22,991.

106. *See id.* at 22,984–86, 22,990.

107. *Id.* at 22,984, 22,991.

108. *See* CTR. FOR FOOD SAFETY & APPLIED NUTRITION (CFSAN), FDA, DRAFT GUIDANCE FOR INDUSTRY: RECOMMENDATIONS FOR THE EARLY FOOD SAFETY EVALUATION OF NEW NON-PESTICIDAL PROTEINS PRODUCED BY NEW PLANT VARIETIES INTENDED FOR FOOD USE 5 (2004), *available at* <http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0369-gdl0001.pdf>.

109. FDA Talk Paper, *supra* note 15.

110. *Id.*

111. *Id.*

the FDA concluded that “any potential risk from the low level presence of such material in the food supply would be limited to the possibility that . . . a new protein . . . might be an allergen or toxin.”¹¹²

The 2004 draft guidance is advisory only, and offers no authority for mandating consultation or for rejecting a new protein. However, the FDCA grants the FDA authority to declare any product containing an unacceptable protein to be adulterated and therefore unmarketable within the United States.¹¹³ Once a GM product developer decides to commercialize a particular new plant variety, the FDA expects the developer to participate in a voluntary pre-market consultation process, as established in the 1992 Statement.¹¹⁴ In November 2004, the FDA claimed that all new GM plant varieties intended for food or feed use that were marketed in the United States completed the consultation process before they entered the market.¹¹⁵ The FDA has stated that it does not believe that new plant varieties under development for food and feed use generally pose any safety or regulatory concerns.¹¹⁶ Nonetheless, the agency expects that the communication with the industry in the early evaluation and voluntary consultation processes will ensure that any potential food safety issues regarding a new protein in a new GM plant variety are resolved prior to any possible inadvertent introduction into the food supply.¹¹⁷

The “Early Food Safety Evaluation” procedure, referenced in the 2004 draft guidance, creates a voluntary program for GM product developers to provide the FDA with information about the food safety of each “new protein” at an early stage in the development of the crop.¹¹⁸ This evaluation for new proteins includes six primary data components (plus a catch-all category), four of which are simple identifiers of the source of the protein.¹¹⁹ Once submitted, the FDA will review the

112. *Id.*

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

114. Draft Guidance for Industry: Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use, 69 Fed. Reg. 68,381, 68,382 (Nov. 24, 2004) (providing notice of the availability of the draft guidance).

115. *See* FDA Talk Paper, *supra* note 15.

116. *See id.*

117. *See id.*

118. Draft Guidance for Industry, 69 Fed. Reg. at 68,382. A “new protein” is defined as “any non-pesticidal protein produced in a new plant variety that is either new to the plant species, or is a native protein that has been produced at a significantly elevated level, and has not been the subject of a completed biotechnology consultation or a completed early food safety evaluation” with the FDA. CFSAN, RECOMMENDATIONS FOR THE EARLY FOOD SAFETY EVALUATION, *supra* note 108.

119. *See* Draft Guidance for Industry, 69 Fed. Reg. 68,383. The primary data components are:

developer's assessments of allergenicity and toxicity to humans and feed-eating animals.¹²⁰ The FDA will then either seek additional information, request voluntary consultation if the protein raises safety concerns, or indicate that the agency has no further questions regarding the protein.¹²¹ An individual new protein will only have to undergo this evaluation once. Later developers can rely on earlier assessments of the protein even when introducing the new protein into another plant or animal species.¹²²

The narrow focus of the voluntary review process demonstrates that even after the 2004 guidance, the FDA's analysis of novel GM products is not a holistic review that seeks out all of the differences between the transgenic organism and its related varieties. Instead, the FDA evaluates only those elements of the new variety that are physically identifiable as different from the primary originating organism and limits its focus to issues of allergenicity and toxicity.¹²³ The FDA did not recognize that the novel GM crops pose a challenge to the existing food-drug categorization process, or that existing law was insufficient to address the regulatory needs of these new products. Instead, regulatory scrutiny focused on the "new protein" and its direct risks to health.¹²⁴ Indirect risks such as environmental impacts posed by these novel organisms are not a part of this analysis.

c. Case Law

There has been very little case law regarding the application of the FDCA definitions to bioengineering products, and the available decisions are deferential to FDA determinations to approve these products. In *Alliance for Bio-Integrity v. Shalala*, the court granted summary judgment to the FDA in a challenge to the agency's assumption of

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1. The name, identity, and function of the new protein(s) produced in the new plant variety;
 2. Data and information as to whether this protein has been safely consumed in foods;
 3. A list of the identity(ies) and source(s) of the introduced genetic material;
 4. A description of the purpose or intended technical effect of the new protein;
 5. An assessment of the amino acid similarity between the new protein and known allergens and toxins;
 6. The overall stability of the protein, and the resistance of the protein to enzymatic degradation using appropriate in vitro assays; and,
 7. Any other pertinent information.

CFSAN, GUIDANCE FOR INDUSTRY, *supra* note 108, at 9.

120. See CFSAN, GUIDANCE FOR INDUSTRY, *supra* note 108, at 13–14.

121. See *id.* at 14.

122. See *id.* at 6.

123. See *id.*

124. See *id.*

“generally recognized as safe” for GM foods.¹²⁵ The court deferred to the FDA’s decision making and expertise under the limited arbitrary and capricious standard for judicial review of agency decision making.¹²⁶ The court explained that “[i]n an area characterized by scientific and technological uncertainty[,] . . . this court must proceed with particular caution, avoiding all temptation to direct the agency in a choice between rational alternatives.”¹²⁷

As recently as March 2006, the District Court for the District of Columbia again deferred to the FDA. In *International Center for Technology Assessment v. Thompson*, the court affirmed the agency’s authority to decide not to regulate the commercial sale of genetically engineered aquarium-use fish, trademarked as “GloFish.”¹²⁸ Although plaintiffs alleged that the fish could be put to unintended uses, and thus readily enter the animal and human food chains,¹²⁹ the court upheld the FDA’s determination that “[i]n the absence of a clear risk to the public health, the FDA finds no reason to regulate these particular fish.”¹³⁰ This high degree of deference to the FDA’s oversight authority emphasizes the importance of effective regulatory processes for addressing the risks posed by GMOs.

2. *Drug Definitions*

The FDCA’s statutory definitions pertaining to drugs focus on the intended use of the product—either to address disease or to affect the structure or function of the body.¹³¹ The drug definition can be particularly problematic in the regulation of GM products since new GM products may affect the body in a fashion unrelated to disease. Without an intended use to cure or treat disease, a GM product will not be classified as a drug, and therefore not be subjected to the strict regulatory scrutiny applied to drugs, despite potential or actual impacts on body functions. This is akin to the difficulties in applying the drug definition to fertility products, which do not address an ailment in the body, but

125. *Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166 (D.D.C. 2000).

126. *Id.*

127. *Id.* at 177 (quoting *Int’l Fabricare Inst. v. EPA*, 972 F.2d 384, 389 (D.C. Cir. 1992)).

128. *Int’l Ctr. for Tech. Assessment (ICTA) v. Thompson*, 421 F. Supp. 2d 1 (D.D.C. 2006). The GloFish experience is explored further below. See *infra* note 279 and accompanying text.

129. See *ICTA*, 421 F. Supp. 2d at 4.

130. Press Release, FDA, FDA Statement Regarding Glofish (Dec. 9, 2003), available at www.fda.gov/bbs/topics/NEWS/2003/NEW00994.html.

131. See Federal Food, Drug, and Cosmetic Act of 1938 § 201(g)(1)(B)–(D), 21 U.S.C. § 321(g)(1)(B)–(D) (2006). In comparison, food and feed definitions focus on product use for nutritive value, taste and aroma. See *Nutrilab, Inc. v. Schweiker*, 713 F.2d 335, 338 (7th Cir. 1983) (explaining the circular definition of “food” in 21 U.S.C. § 321(f)); see also FDCA § 201(w); 21 U.S.C. § 321(w) (defining animal feed).

instead seek to enhance natural and disease-free functioning.¹³² Such definitional loopholes can lead to minimal or no FDA oversight of a GM product despite serious risks to human or livestock health.

a. Drugs

The FDA is responsible for review of new drug products prior to their approval for sale in the U.S. marketplace.¹³³ The FDA has adopted a rigorous drug approval process, under the authority of the FDCA, to protect the public from drugs that may be unsafe or ineffective for their intended uses.¹³⁴ Under this structure, drugs containing genetically engineered components receive at least the same scrutiny as conventional drug components. This high standard of scrutiny stands in sharp contrast to the presumption of safety for foods, even foods created by genetic modification.

The human drug regulatory process depends upon the classification of a candidate product as a “drug” or a “new drug.” These definitions encompass both drugs intended for animal use and those for human use. “Drugs” are “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.”¹³⁵ Articles “intended to affect the structure or any function of the body of man or

132. See Christine Willgoos, *FDA Regulation: An Answer to the Questions of Human Cloning and Germline Gene Therapy*, 27 AM. J.L. & MED. 101, 120 (2001).

133. Greenberg, *supra* note 59, at 303.

134. See generally Federal Food, Drug, and Cosmetic Act of 1938 §§ 201, 505, 21 U.S.C. §§ 321, 355 (2006).

135. FDCA § 201(g)(1)(B), 21 U.S.C. § 321(g)(1)(B); see also *Pharmanex v. Shalala*, 221 F.3d 1151, 1156 (10th Cir. 2000) (holding that the FDCA drug definition applies to active ingredients as well as finished drug products); *United States v. Undetermined Quantities of Bottles*, 22 F.3d 235, 237 (10th Cir. 1994) (affirming definition of pet food additive containing antibiotic intended to reduce pet odors as a “drug” for FDCA purposes); *United States v. Sullivan*, 332 U.S. 689, 695 (1948) (treating mislabeled sulfathiazole as a “drug” under the FDCA); *United States v. Undetermined Quantities of Articles of Drug, Street Drug Alternatives*, 145 F. Supp. 2d 692, 703–03 (D. Md. 2001) (rejecting attempt to label herbal “drug alternatives” as “dietary supplements” when alternate drugs were made specifically to mimic effects of street drugs). *But see Nat’l Nutritional Foods Ass’n v. Matthews*, 557 F.2d 325, 333 (2d Cir. 1977) (holding FDA’s classification of high dosage vitamins as “drugs” was “arbitrary and capricious and not in accordance with law”).

Because most “biologics” fit within the definition of “drug,” these products are also regulated under the FDCA. These are a wide range of products, including products of genetic engineering, such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Gene-based and cellular biologics are at the cutting edge of biomedical research. Biological products are approved for marketing under provisions of the Public Health Service Act. The FDA’s Center for Biological Evaluation and Research (CBER) has authority to regulate certain drugs closely related to biologics, such as the anticoagulants included in plastic blood collection containers. See FDA, CBER Frequently Asked Questions, <http://www.fda.gov/cber/faq.htm> (last visited Jan. 18, 2007).

other animals,” other than food, and articles “intended for use as a component of any such article” are also considered to be drugs.¹³⁶ This definition also encompasses any article recognized in a specified official U.S. pharmacopoeia or formulary. “Dietary ingredients” and “dietary supplements” are separately defined and regulated.¹³⁷

A “new drug” is “any drug . . . the composition of which is . . . not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof.”¹³⁸ A drug that has been deemed safe and effective following investigation, but has not otherwise been used to a material extent or for a material time under the conditions studied, will also be considered a new drug.¹³⁹ Thus, an existing product whose safety and effectiveness has not been generally recognized by experts may be considered a new drug under the FDCA.¹⁴⁰

Drug regulation under the FDCA focuses primarily on the new drug approval authority and process, which consists of approval of an initial application followed by three clinical trial phases.¹⁴¹ The FDA sometimes takes years to review and approve a New Drug Application (NDA), the

136. FDCA § 201(g)(1)(C)–(D), 21 U.S.C. § 321(g)(1)(C)–(D).

137. FDCA §§ 201(g)(1), 201(ff), 403(r)(1)(B), (r)(3), (r)(5)(D) & (r)(6), 21 U.S.C. §§ 321(g)(1), 321(ff), 343(r)(1)(B), (r)(3), (r)(5)(D) & (r)(6). Dietary supplements are generally regarded as foods under 21 U.S.C. § 321(ff).

138. FDCA § 201(p)(1), 21 U.S.C. § 321(p)(1) (for human drugs, also creating an exemption for drugs in use prior to the FDCA’s enactment in 1938 but still subject to the 1906 Pure Food and Drug Act, so long as the current labeling still contains the same conditions of use). *See* United States v. Sage Pharm., Inc., 210 F.3d 475, 479 (5th Cir. 2000) (discussing FDA prosecution to prevent sale and marketing of a “new drug” until it received approval); United States v. 225 Cartons, More or Less, of an Article or Drug, 871 F.2d 409, 420 (3d Cir. 1989) (finding combination drugs to be “new drugs” under FDCA). New animal drugs are defined separately, but very similarly, in 21 U.S.C. § 321(v).

139. *See* FDCA § 301(p)(2), 21 U.S.C. § 321(p)(2) (2006).

140. *See* United States v. 50 Boxes More or Less, 909 F.2d 24, 28 (1st Cir. 1990) (holding that although drug had been sold to the public for thirty-five years, it had never been generally recognized by experts as safe and effective for the intended use, and so was considered a “new drug” under the FDCA).

141. *See* 21 C.F.R. §§ 312.20–312.38 (2006). Ordinarily, experimental drugs may not be employed on human subjects without prior FDA oversight through the Investigational New Drug (IND) application procedure. *See id.* § 312.20(b). The primary aim of Phase I trials is to gather pharmacology and toxicity information related to possible adverse drug effects on humans. If negative effects occur, the drug may be rejected if its therapeutic or commercial potential are unacceptably compromised. Phase II trials are conducted using a controlled, experimental methodology in order to determine drug efficacy, although positive results in Phase II tests generally do not establish efficacy in themselves. The rationale for additional testing after Phase II is based on the lack of statistical credibility of the small-scale Phase II studies. In Phase III studies, hundreds or thousands of research subjects usually are recruited to participate in large-scale, controlled trials of the experimental medication to collect extensive data regarding dose-response, adverse effects, and drug interactions. *See* 21 C.F.R. § 312.21; Greenberg, *supra* note 59, at 305. Following Phase III, the drug developer can submit its clinical trial research data to the FDA in the New Drug Application (NDA). *See* 21 C.F.R. § 314.50.

final step before sale of the new drug is allowed in the U.S. marketplace.¹⁴² Considering the speed of innovation for novel transgenic organisms, the drug approval process could pose an obstacle to product development. New product developers are therefore incentivized to assert nondrug intended uses for their products in addition to, or instead of, initiating the new drug application process. As discussed, nondrug uses for GM products are subject to much less rigorous regulatory scrutiny than are drug uses. The GM product can thus avoid the drug approval process, thereby speeding regulatory approval and maximizing immediate marketing opportunities.

b. Animal Drugs

The FDA regulates animal drugs as well as drugs intended for human use. A new animal drug must go through the New Animal Drug Application (NADA) or Investigational New Animal Drug (INAD) process to receive FDA approval, a procedure similar to that required for human drugs.¹⁴³ Under the FDCA, a “new animal drug” (NAD) is “any drug intended for use for animals other than man, including any drug intended for use in animal feed.”¹⁴⁴

A new animal drug may not be introduced into interstate commerce unless the FDA has approved the corresponding NADA or INAD.¹⁴⁵ The NADA must demonstrate the safety and effectiveness of the product.¹⁴⁶ The burden of proving that the drug meets this standard is entirely on the sponsor.¹⁴⁷ Thus, as with human drugs, the standard of review for animal drugs, including genetically engineered animal drugs, is much higher than

142. See Greenberg, *supra* note 59, at 306.

143. See Coordinated Framework for the Regulation of Biotechnology, 51 Fed. Reg. 23,302, 23,309 (June 26, 1986); Federal Food, Drug, and Cosmetic Act of 1938 § 512, 21 U.S.C. § 360(b) (2006).

144. FDCA § 201(v), 21 U.S.C. § 321(v). This definition excludes drug-containing animal feed if: (1) its composition is such that the drug is not generally recognized by qualified experts as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof; or (2) the feed, although recognized as safe and effective in investigation circumstances, has not been used to a material extent or for a material time under the conditions prescribed, recommended, or suggested in the labeling, other than in the investigations. In these circumstances, the drug-containing feed product generally would not qualify for approval as a new animal drug and could not be marketed as such. However, for long-existing animal feeds with drug components, if the animal feed product was subject to the Food and Drug Act of 1906 prior to 1938, and its labeling contained the same representations concerning the conditions of its use, the product will not be deemed to be a “new animal drug.”

145. See FDCA § 512(a)(1), 21 U.S.C. § 360b(a)(1). A new animal drug enters the FDA regulatory process when the sponsor submits a Notice of Claimed Investigational Exemption, referred to as an Investigational New Animal Drug (INAD), before distributing the new drug for clinical (effectiveness) tests in animals. See 21 C.F.R. § 311.1(b)(4) (2006).

146. See FDCA § 512(a)(1), 21 U.S.C. § 360b(a)(1).

147. See FDCA § 512(b)(1), 21 U.S.C. § 360b(b)(1).

that for food or feed products.¹⁴⁸ A GM product intended for use as animal feed would receive much less scrutiny than a product intended to diagnose, treat, or prevent an animal illness. However, regardless of classification as a food or drug, the recipient person or animal ingests the novel GM product, and is subjected to the risks presented by that product.

The FDA can assert primary regulatory authority over a GMO by virtue of its new animal drug authority.¹⁴⁹ The FDA interprets the pertinent NAD statutes to authorize the regulation of GMOs intended for human or livestock food uses because the inserted genes, and the proteins they produce, may affect the “structure and function” of the recipient animal in a manner analogous to the impact of a veterinary drug.¹⁵⁰ Therefore, the genetic modification itself may be considered a new animal drug.¹⁵¹ However, this claim of authority over GMOs conflicts with the FDA’s (and the Coordinated Framework’s) presumption of safety for GM products in the absence of evidence of heightened risk because of the genetic manipulation.

In the NAD approval process, the FDA predominantly concerns itself with questions of how consumption of the new drug might directly affect human health, rather than on animal health, or the environmental impact of the NAD or its source.¹⁵² Under the FDCA, a NAD’s safety is defined with “reference to the health of man or animal.”¹⁵³ Therefore, as part of the NAD safety assessment the FDA must consider environmental effects of the NAD that would directly or indirectly affect the health of humans or animals.¹⁵⁴ The FDA has no authority to consider potential adverse environmental effects that are purely environmental in that they do not pose risk of direct or indirect harm to man or animals.¹⁵⁵

However, because granting an INAD or NADA is a federal action under NEPA, the FDA must comply with NEPA as it carries out its new animal drug approval process. INADs and NADAs require submission of

148. Compare the drug approval process to the food adulteration review discussed *supra* note 93 and accompanying text.

149. See *supra* note 144 and accompanying text; see also Federal Food, Drug, and Cosmetic Act of 1938 § 512, 21 U.S.C. § 360(b) (2006); Coordinated Framework for the Regulation of Biotechnology, 51 Fed. Reg. 23,302, 23,309 (June 26, 1986).

150. OFFICE OF SCI. & TECH. POL’Y (OSTP), EXECUTIVE OFFICE OF THE PRESIDENT, CASE STUDY NO. I: GROWTH-ENHANCED SALMON, CASE STUDIES OF ENVIRONMENTAL REGULATIONS FOR BIOTECHNOLOGY 13–14 (2001), available at <http://www.ostp.gov/html/012201.html>.

151. *Id.*

152. Rebecca Bratspies, *Glowing In The Dark: How America’s First Transgenic Animal Escaped Regulation*, 6 MINN. J.L. SCI. & TECH. 457, 474 (2005).

153. See FDCA § 201(u), 21 U.S.C. § 321(u).

154. See *id.*; see also OSTP, GROWTH-ENHANCED SALMON, *supra* note 150, at 14.

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

a claim of categorical exclusion or an environmental assessment (EA).¹⁵⁶ The EA should provide information relevant to determining if environmental harms resulting from use of the NAD could adversely affect human or animal health, thereby facilitating FDA's review of environmental risks as a part of its safety review under the FDCA.¹⁵⁷ This review could result in the FDA deeming the drug unsafe. In addition, the FDA can use its authority under the FDCA to enforce compliance with mitigations required as a condition of product approval, or to reject or withdraw approval of products that cause unexpected and immitigable environmental impacts that adversely affect the health of humans or animals.¹⁵⁸

In practice, however, the FDA has not consistently exercised its new drug approval power under the FDCA to conduct thorough screening of genetically engineered products for risks to human or animal health. In fact, the FDA declined any review of the first transgenic animal to be offered for sale in the United States, the GloFish, as explored in Part V, below.¹⁵⁹ Although the green fluorescent protein inserted into the DNA of these fish could be considered to alter the structure and function of these fish, thus qualifying for animal drug analysis, the FDA focused on the intended use of the fish as aquarium pets and denied authority to review. However, the President's Office of Science and Technology Policy asserts that the insertion of foreign genes into growth-enhanced salmon, also discussed in Part V, opens these fish to new animal drug analysis.¹⁶⁰ This inconsistency in the exercise of the new drug approval authority is deleterious to industry and consumer confidence in FDA regulation of GMOs.

c. Adulteration and Misbranding of Drugs

Following FDA approval, a drug may still be rejected or removed from the market if the drug product is deemed to have been adulterated.¹⁶¹ Similar to foods, drugs are considered adulterated if strength, quality, or purity differ from official standards.¹⁶² Because drugs undergo such a thorough review for safety and efficacy prior to being approved for marketing, adulteration plays a lesser role in drug

156. See 21 C.F.R. §§ 25.15, 511.1(b)(10), 514.1(b)(10) (2006).

157. OSTP, GROWTH-ENHANCED SALMON, *supra* note 150, at 14 (outlining the expected use of the environmental analysis in the FDA's review of GM salmon).

158. See FDCA § 512, 21 U.S.C. § 360(b).

159. See *infra* note 280 and surrounding text.

160. OSTP, GROWTH-ENHANCED SALMON, *supra* note 150, at 13.

161. See Federal Food, Drug, and Cosmetic Act of 1938 §§ 301, 501(b), 21 U.S.C. §§ 331, 351(b) (2006). The analysis of whether a drug incorporating a GM product qualifies as adulterated applies equally to human and animal drugs.

162. See FDCA § 501(b), 21 U.S.C. § 351(b).

regulation than food regulation. Drugs are highly scrutinized prior to consumer use, regardless of whether they contain GM products. In contrast, the ability to declare a GM food product adulterated and address a previously unrecognized risk is especially valuable to the FDA since these products may have received very little regulatory review before they became publicly available for consumption.

The FDA will also reject a drug, genetically engineered or not, from commercial marketing if the product is misbranded.¹⁶³ “Misbranding” includes using false or misleading labels, packaging, or containers.¹⁶⁴ The debate over whether GM products are misbranded unless they are specially labeled for consumers applies for drugs just as it does for foods.¹⁶⁵

3. *Combination Products*

The FDA had established a special methodology to regulate products that combine drugs, biologics,¹⁶⁶ and devices.¹⁶⁷ However, although many GM products raise the same safety concerns as combination products, they are left largely unregulated under the combination product regime.

The FDA established the Office of Combination Products to handle agency oversight of these products in 2002, as required by the Medical

163. See FDCA § 502, 21 U.S.C. § 352 (classifying misbranded drugs and devices); see also cases cited *supra* note 85.

164. FDCA § 502, 21 U.S.C. § 352.

165. See *supra* note 86. Although this debate is rigorous within the academic and legislative arenas, it remains beyond the scope of this Comment.

166. A biologic is a “biological product,” defined in the Public Health Service Act as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

42 U.S.C. § 262(i) (2006). Biologics are regulated separately by the FDA from drugs, and are not required to undergo the new drug approval process of 42 U.S.C. § 262(j).

167. See 21 C.F.R. § 3.2(e) (2006). As defined, the term combination product includes: products comprising two or more of these components (drugs, biologics or devices) that are physically, chemically, or otherwise combined or mixed and produced as a single entity; two or more of these products packaged together in a single package or as a unit; separately packaged products where both are required to achieve the intended use, indication, or effect, and the labeling of the approved product would need to be changed to reflect a change in intended use, dosage, etc. due to the combination; or any investigational drug, device, or biological product packaged separately but intended for use only with another individually specified investigational drug, device, or biological product to achieve the intended effect. See also Federal Food, Drug, and Cosmetic Act of 1938 § 503(g), 21 U.S.C. § 353(g) (2006); *Bracco Diagnostics v. Shalala*, 963 F. Supp. 20, 28 (D.D.C. 1997) (holding injectable contrast imaging agents for use with diagnostic ultrasound equipment meet both definition of “drug” and “device” under FDCA and therefore FDA may determine how to treat such agents, as long as it treats similar products similarly). But see *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 125–26 (2000) (holding FDA lacks jurisdiction to regulate tobacco products as a combination of both “drugs” and “devices”).

Device User Fee and Modernization Act.¹⁶⁸ The FDA also promulgated regulations and issued guidance documents to set agency policy and to instruct industry regarding combination products.¹⁶⁹ The authority for these regulations rests in the FDCA.¹⁷⁰ The formal process for determining jurisdiction over both combination and single entity products is accomplished through the FDA's Request for Designation process.¹⁷¹

The FDA explains that the impetus for establishing the new Office of Combination Products was the fact that combination products "are increasingly incorporating cutting edge, novel technologies."¹⁷² Further, the FDA expects "to receive significantly more combination products for review as technological advances continue to merge therapeutic products and blur the historical lines of separation between FDA's medical product Centers."¹⁷³ Because combination products are usually reviewed under different regulatory authorities, often by different FDA Centers, these products raise concerns about

the consistency, predictability, and transparency of the assignment process; issues related to the management of the review process when [multiple] FDA Centers have review responsibilities for a combination product; lack of clarity about the post-market regulatory controls applicable to combination products; and lack of clarity regarding certain Agency policies, such as when applications to more than one Agency Center are needed.¹⁷⁴

There are many commonalities between the FDA's concerns regarding the regulation of combination products and genetically engineered organisms. Yet, the FDA has chosen not to regulate GM products through either the combination product regime or to create a similar system tailored to the GM arena. The FDA has not consolidated its oversight of genetically engineered foods and drugs into a single review regimen to be followed by all interested agencies.¹⁷⁵ The recommendations part of this Comment further analyzes this decision.

B. The Role of Intended Use

The FDA determines whether a GM product fits within the definition of a food, drug, or other category based on the intended use of

168. See FDA, Overview of the Office of Combination Products, *supra* note 5; see also Medical Device User Fee and Modernization Act of 2002, Pub. L. No. 250, 116 Stat. 1588.

169. See the current listing of FDA guidance documents and procedures at the Office of Combination Products internet site at <http://www.fda.gov/oc/combination/>.

170. See Federal Food, Drug, and Cosmetic Act of 1938 § 503(g), 21 U.S.C. § 353(g) (2006).

171. See 21 C.F.R. § 3.7 (2006). See generally 21 C.F.R. pt 3.

172. FDA, Overview of the Office of Combination Products, *supra* note 5.

173. *Id.*

174. *Id.*

175. See *supra* text accompanying notes 71–74 for a description of the fragmented oversight of genetically engineered food and drugs.

the product stated by the developer or manufacturer.¹⁷⁶ The FDA is not bound by the manufacturer's subjective claims of intent, but can conclude what the actual intended use will be based on objective evidence.¹⁷⁷ Nonetheless, in practice, intended use is determined largely based on the claims made on product labels and in product marketing and advertising.¹⁷⁸ For example, a product otherwise appearing to be a conventional food or dietary supplement could be regulated as a drug if the product's advertising or marketing claims demonstrate an intent that the product be used in a manner falling within the drug definition.¹⁷⁹

The reliance on a manufacturer's or developer's assertions of intended use leads to multiple problems. The application of intended use opens the regulatory agency to manipulation by product developers or manufacturers, leads to inconsistent treatment of similar products, and creates a redundant and inefficient regulatory process.

First, it is possible for a developer to enter a transgenic product into the U.S. marketplace without FDA approval or oversight if the intended use of the product is for a nonfood or nondrug purpose.¹⁸⁰ The regulatory authority over transgenics intended for pet or industrial uses, while uncertain, is definitely weaker than what has been established for food and drugs.¹⁸¹ This allows a developer to introduce a GM product into the United States for one use, but either by design or circumstance the product will actually be used for other purposes. Once a product is prevalent in the U.S. marketplace, the FDA will have a more difficult time either withdrawing the product or ensuring that it is not used for unapproved purposes.

Second, the focus on intended use could lead to different standards for the risk assessment of a single component of a GMO. This can result in inconsistent regulatory requirements or agency decisions. For example, a single GMO might produce both food and drug products. Under the

176. See Federal Food, Drug, and Cosmetic Act of 1938 § 201(g)(1)(B), 21 U.S.C. § 321(g)(1)(B) (2006) (definition of drug focusing on intended use); Hahn, *supra* note 78, at 307–09 (discussing the distinction between foods, drugs, and dietary supplements); Barbara A. Noah, *Foreword: Dietary Supplement Regulation in Flux*, 31 AM. J.L. & MED. 147, 149 n.12 (2005) (explaining the FDA focus on intended use in categorizing products).

177. See *United States v. Storage Spaces Designated Nos. "8" & "49"*, 777 F.2d 1363, 1366 (9th Cir. 1985) (holding vendor's intended application for product may be derived from any relevant source, including product labels and any promotional material); see also *United States v. Kasz Enters., Inc.*, 862 F. Supp. 717, 720–21 (D.R.I. 1994) (affirming that promotional materials for hair care products were properly used to determine whether product was a "drug" under the FDCA); *United States v. Vital Health Prods.*, 786 F. Supp. 761, 766 (E.D. Wis. 1992) (holding that using claims in product literature to determine if products are "drugs" under FDCA is proper).

178. See Hahn, *supra* note 78, at 306.

179. See *id.* at 307.

180. See discussion of the GloFish in Part V.B.1.

181. *Id.*

current FDCA structure, the products would receive different levels of regulatory analysis, although they contain the same novel transgenic protein expressions. Conceptually, the idea that a new drug should receive more scrutiny than a longstanding food product is sound. However, when two products have the same source, that source is new and offers no history of safe consumption, and both the food and drug product are to be ingested by the user, dependence on a use-based distinction to estimate risk potentials becomes less reasonable. Rather than basing the level of regulatory scrutiny on the intended use of each GM product, comprehensive scrutiny of the risks and benefits likely presented by the GMO as a whole is more appropriate. The traditional labels of “foods” or “drugs” should not have so much power in the review process of innovative and technologically complicated products developed from novel transgenic organisms.

Finally, by regulating GMOs and their derivatives on a product-by-product, intended-use basis, the Coordinated Framework and FDCA create a strong likelihood of redundant or inadequate regulatory review. Product developers must complete the appropriate product approval process for each new use to which a GMO might be applied. Each agency unit receiving a product approval application must consider the product anew under the regulatory review process for that particular use. Even if the agencies cooperate, and share their assessment data from past products, this remains an unnecessarily duplicative process. To minimize such duplication, the FDA has implemented processes under which a new GM protein approved for use in one plant variety will not require assessment for future uses in that or related plant varieties because FDA has already determined that the protein is safe.¹⁸² While this is a move toward more efficient regulation, allowing a single review to satisfy all regulatory inquiry regarding a GM protein, regardless of the differences between current and future uses, is inadequate regulatory oversight. Genetic modifications may cause unexpected and divergent changes to each organism in which the protein is inserted. Critics of GMOs and the general public would not be comforted by the idea that later generation GM products would receive no scrutiny before commercial marketing, since the novel protein they carry was previously approved, in an unrelated GMO, absent a showing of risk.¹⁸³ The public would be better served by a single, comprehensive review of all of the risks reasonably posed by a GMO and its derivative products.

182. See *supra* note 122 and *infra* note 222 and surrounding discussion.

183. For example, a fish-based protein approved for insertion in a different fish intuitively presents less likelihood of unexpected harm than the insertion of that same protein into a strawberry, regardless of the fact that the protein was considered safe in the initial FDA review.

IV. DEMONSTRATED FAULTS OF THE COORDINATED FRAMEWORK

A. *Substantial Equivalence*

Under the Coordinated Framework, the federal regulatory structure overseeing GM food products operates under “a presumption of safety,”¹⁸⁴ so long as the GM product is substantially equivalent to the original. The United States has embraced the doctrine of “substantial equivalence” to address the scientific uncertainty regarding the types and degrees of risk presented by GM food products.¹⁸⁵ The substantial equivalence determination is based solely on a specific comparison of each of the physical characteristics and components of the modified organism with those of its conventional counterpart.¹⁸⁶ Only those features that are shown to be physically different from the conventional counterpart are subjected to scrutiny.¹⁸⁷ Unless specific evidence is presented to defeat a determination of substantial equivalence, a GM food product is subjected to the same regulatory oversight as the unmodified product to which it is deemed equivalent.¹⁸⁸

Although GM products are likely to have been altered to an extent that is sufficiently “novel” to qualify for patent protection for the developer,¹⁸⁹ the vast majority of food products submitted for commercial marketing thus far have continued to meet the United States’ definition of substantial equivalence, thus incurring no special regulatory scrutiny.¹⁹⁰

184. See Coordinated Framework for the Regulation of Biotechnology, 51 Fed. Reg. 23,302 (June 26, 1986); see also Thomas O. McGarity, *Seeds of Distrust: Federal Regulation of Genetically Modified Foods*, 35 U. MICH. J.L. REFORM 403, 429 (2002) (describing how the presumption of safety is an extension of the doctrine of substantial equivalence). This presumption of safety has not been adopted internationally, and many countries operate from a much more conservative risk assessment basis. See *infra* note 207 and surrounding discussion.

185. See Kysar, *supra* note 4, at 556–57 (distinguishing the current product based regulation of GMOs from any attempt to regulate the processes of genetic engineering); McGarity, *supra* note 184, at 429 (explaining that “[t]he baseline assumption of the substantial equivalence doctrine is that there is nothing inherently novel about plant breeding through modern genetic engineering.”); John S. Applegate, *The Prometheus Principle: Using the Precautionary Principle to Harmonize the Regulation of Genetically Modified Organisms*, 9 IND. J. GLOBAL LEG. STUD. 207, 232 (2001); see also Coordinated Framework, 51 Fed. Reg. at 23,302.

186. See ORG. FOR ECON. CO-OPERATION & DEV., SAFETY EVALUATION OF FOODS DERIVED BY MODERN BIOTECHNOLOGY: CONCEPTS AND PRINCIPLES 14 (1993); Kysar, *supra* note 4, at 557 (outlining the “difficulty in determining the class of compositional and other tangible characteristics to provide the benchmarks for the substantial equivalence determination.”).

187. See Gregory N. Mandel, *Gaps, Inexperience, Inconsistencies, and Overlaps: Crisis in the Regulation of Genetically Modified Plants and Animals*, 45 WM. & MARY L. REV. 2167, 2242 (2004).

188. See ORG. FOR ECON. CO-OPERATION & DEV., *supra* note 186, at 14–16 (1993) (introducing the “substantial equivalence” concept); see also Kysar, *supra* note 4, at 557.

189. Kysar, *supra* note 4, at 557.

190. See *id.*

However, developments in biotechnology now enable the creation of a new generation of transgenic products so novel that a conventional counterpart cannot reasonably be said to exist. This trend will continue because the potential for creativity in biotechnology is unlimited. At some point, determining which of the several gene-contributors to a novel transgenic organism should be used as a conventional counterpart for substantial equivalence comparison will be either arbitrary or nonmeaningful.

In keeping with the substantial equivalence doctrine, the Coordinated Framework adopted as a foundational principle the assumption that the processes of biotechnology are not inherently risky, and thus, only the products of biotechnology require regulatory oversight, not the processes themselves.¹⁹¹ Without an identifiable alteration in the physical features and characteristics of the end product, the substantial equivalence doctrine assumes that the processes utilized to effect nondistinguishable modifications in an organism's genetic expression are inconsequential and require no additional oversight or concern from regulators or consumers.¹⁹² Thus, the products of biotechnology should be regulated in the same manner as conventionally created products.¹⁹³ In its final Coordinated Framework policy statement, the FDA announced:

Although there are no statutory provisions or regulations that address biotechnology specifically, the laws and regulations under which the agency approves products places the burden of proof of safety as well as effectiveness of products on the manufacturer. The agency possesses extensive experience with these regulatory mechanisms and applies them to the products of biotechnological processes. In this notice, FDA proposes no new procedures or requirements for regulated industry or individuals. Rather, the administrative review of products using biotechnology is based on the intended use of each product on a case-by-case basis.¹⁹⁴

Application of the substantial equivalence concept is demonstrated in a 2003 U.S. Department of Agriculture (USDA) draft risk assessment addressing the hazards of cloned livestock, which analyzes risk using a "Compositional Analysis Method," under which regulators are to assume that "food products from healthy animal clones and their progeny that are not materially different from corresponding products from conventional animals are as safe to consume as their conventional

191. See Coordinated Framework for the Regulation of Biotechnology, 51 Fed. Reg. 23,302, 22,303 (June 26, 1986); see also Mandel, *supra* note 187, at 2216; Applegate, *supra* note 185, at 232. The processes of biotechnology are the methods and mechanisms used to achieve physical intervention in a gene strand and growth of the new GM organism.

192. See Mandel, *supra* note 187, at 2216, 2242.

193. See Coordinated Framework, 51 Fed. Reg. at 23,302-03, 23,309, 23,336; see also Mandel, *supra* note 187, at 2242; Applegate, *supra* note 185, at 232.

194. Coordinated Framework, 51 Fed. Reg. at 23,310.

counterparts.”¹⁹⁵ Material difference would require not only that the component be physically different from its conventional analog, but also that the difference be relevant to the risks posed by that component.¹⁹⁶ Thus, proof that a component derived from a cloned animal or its offspring presents a new or heightened health hazard is required before that specific food product may be considered unsafe.

In December 2006, the FDA again relied on a specific comparison approach in another draft risk assessment that focused on the safety of foods derived from cloned animals.¹⁹⁷ To assess the risks cloning posed to food consumption, the FDA’s Center for Veterinary Medicine (CVM) conducted a two-pronged analysis, comparing clone health and clone-derived food products with those of traditionally bred animals.¹⁹⁸ Under the Critical Biological Systems Approach, the CVM systematically reviewed the health of the animal clone or its progeny, based on the presumption that healthy animals are likely to produce safe food products.¹⁹⁹ Next, under the Compositional Analysis Method used in the 2003 risk assessment, the CVM compared the individual components of edible products with identified comparators.²⁰⁰

The study concluded that cloned beef, swine, goats, and their progeny posed no increased risk over their traditional analogs.

Extensive evaluation of the available data has not identified any food consumption risks or subtle hazards in healthy clones of cattle, swine, or goats. Thus, edible products from healthy clones that meet existing requirements for meat and milk in commerce pose no increased food consumption risk(s) relative to comparable products from sexually-derived animals. The uncertainties associated with this judgment are a function of the empirical observations and underlying biological processes contributing to the production of clones. There is less

195. FDA, ANIMAL CLONING: A RISK ASSESSMENT: DRAFT EXECUTIVE SUMMARY 5 (2003), *available at* <http://www.fda.gov/cvm/Documents/CLRAES.doc>; *see also* Kysar, *supra* note 4, at 557–58.

196. *See* Kysar, *supra* note 4, at 557–58.

197. CTR. FOR VETERINARY MED., FDA, ANIMAL CLONING: A DRAFT RISK ASSESSMENT 3–8 (2006), *available at* http://www.fda.gov/cvm/Documents/Cloning_Risk_Assessment.pdf. The cloned animals were created through somatic cell nuclear transfer, a form of genetic engineering that does not involve the introduction of recombinant genetic material from other sources. Because no exogenous genes are introduced into the cloned animals, the FDA’s underlying assumption regarding potential hazards is that anomalies observed in animal clones are due to incomplete or inappropriate reprogramming of the donor cells. Therefore, any hazards leading to food consumption risks would be subtle, allowing an animal clone to develop with apparently normal functions but with unrecognized physiological anomalies including altered expression of key proteins affecting the nutritional content of food, possibly leading to dietary imbalances.

198. *Id.* at 4–6.

199. *Id.* at 5.

200. *Id.*

uncertainty about the health of clones as they age and have more time to exhibit the full range of functionality expected of breeding stock.²⁰¹

The CVM Director, Stephen F. Sundlof, explained that “[b]ased on FDA’s analysis of hundreds of peer-reviewed publications and other studies on the health and food composition of clones and their offspring, the draft risk assessment has determined that meat and milk from clones and their offspring are as safe as food we eat every day.”²⁰²

Despite its assertions of food safety, the 2006 clone risk assessment was unable to determine if edible products from perinatal bovine or sheep clones posed human food consumption risks because there was insufficient information on the health status of the clones to draw conclusions about potential risks from the consumption of derivative food products from unborn or newborn clones.²⁰³ Just as the inability to claim any existing organism as a conventional counterpart defeats the specific comparison risk analysis, the lack of experience with a transgenic organism also inhibits this approach to risk assessment. The 2006 clone risk assessment demonstrates that specific comparison risk assessment is ineffective when only a limited number of transgenic organisms of that type are available to study, or there are no data regarding the performance of that specific genetically engineered organism over time.

B. Reliance on Existing Law

The Coordinated Framework also formalized the assumption that existing laws are sufficient for the regulation of GM products.²⁰⁴ This is a logical offshoot of the presumption that the products of genetic engineering are no different from their conventional counterparts. The Coordinated Framework expected that existing regulations for foods, crops, medicines, and pesticides²⁰⁵ could be applied to the products of genetic engineering. Implicit in the decision to regulate GM products under existing statutes is the belief that the products of genetic engineering, be they plant or animal, or foods or drugs, are not significantly different from their conventional counterparts. A 1987 National Academy of Sciences report explicitly stated this view.

- 1) There is no evidence of unique hazards either in the use of recombinant DNA techniques, or in the transfer of genes between unrelated organisms.

201. *Id.* at 14–15.

202. Press Release, FDA, FDA Issues Draft Documents on the Safety of Animal Clones: Agency Continues to Ask Producers and Breeders Not to Introduce Food from Clones into Food Supply (Dec. 28, 2006), *available at* <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01541.html>.

203. FDA, ANIMAL CLONING RISK ASSESSMENT, *supra* note 195, at 10–15.

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

205. *See* Applegate, *supra* note 185, at 232.

- 2) The risks associated with the creation and use of genetically engineered organisms are the same in kind as those associated with the introduction of either unmodified organisms, or organisms modified by other methods.
- 3) Assessment of the risks of introducing bioengineered organisms into the environment should be based on the nature of the organism and the environment into which it is introduced, not on the method by which it was produced.²⁰⁶

Thus, the Coordinated Framework considers each element of a GM product to be substantially equivalent to that element in the progenitor organism. The protein introduced is the physical difference between the conventional organism and the transgenic variety, and so this protein will be the focus of the regulatory review. No special evaluation of how the newly introduced element in the novel transgenic organism is expressed and interacts with the new organism, beyond a basic physical comparison, is required.

Were the agencies to closely adhere to the Coordinated Framework's presumption of safety and dependence on existing law, they would be limited in their ability to sponsor or rigorously evaluate new scientific research into the full spectrum of potential biotechnology risks. Such research might militate for a different regulatory approach to biotechnology risk management, but under the dead-hand control of the Coordinated Framework, the agencies would be unable to seek revision or strengthening of existing law to address identified regulatory deficiencies.

The presumption of safety for GM products embraced by the Coordinated Framework stands in contrast to the more conservative approach adopted by many international government and nongovernment entities, U.S. state and local governments, and domestic environmental and scientific organizations. Many entities interested in public safety and risk tolerance have adopted a "precautionary principle" approach to regulating the potential hazards of genetic engineering.²⁰⁷ The precautionary principle "embraces the idea that scientific certainty should not be required before governments take preventative action against potentially serious environmental harms."²⁰⁸ This principle is at the heart of the Greenpeace statement on genetic engineering.

206. NAT'L ACAD. OF SCI., INTRODUCTION OF RECOMBINANT DNA-ENGINEERED ORGANISMS INTO THE ENVIRONMENT: KEY ISSUES (1987). *See also* Exercise of Federal Oversight Within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment, 57 Fed. Reg. 6753 (Feb. 27, 1992) (re-confirming the assumptions of genetic modification safety by the Office of Science and Technology Policy).

207. *See* Applegate, *supra* note 185, at 246-58.

208. Lesley K. McAllister, *Judging GMOs: Judicial Application of the Precautionary Principle in Brazil*, 32 ECOLOGY L.Q. 149, 150 (2005).

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While scientific progress on molecular biology has a great potential to increase our understanding of nature and provide new medical tools, it should not be used as justification to turn the environment into a giant genetic experiment by commercial interests. The biodiversity and environmental integrity of the world's food supply is too important to our survival to be put at risk.²⁰⁹

However, different entities and organizations hold a spectrum of opinions regarding the appropriate level of precaution required to address GM uncertainties. As explained by Professor Gary Marchant, "Based on the maxim 'better safe than sorry,' the [precautionary principle] seeks to formalize the application of precaution to regulatory decision making, even though no standard definition or wording of the principle has yet to emerge."²¹⁰

The merits of the precautionary principle are the subject of tremendous academic and regulatory debate.²¹¹ However, the ability of this principle to accommodate a wide variety of risks illuminates a weakness of the Coordinated Framework. The precautionary principle takes a macroscopic view of potential risks, allowing consideration of indirect, environmental, and latent hazards in risk assessment.²¹² For example, an authoritative statement of policy implementing the precautionary principle appears in the 1992 Rio Declaration on Environment and Development: "Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."²¹³ Due to its exclusive focus on end-product uses and risks to human and livestock health, the Coordinated Framework does not specifically address environmental risks posed by the intended or unintended release of novel genetically modified organisms.²¹⁴ The failure of the Coordinated Framework to address environmental risks will be considered in the analysis of the current U.S. regulatory structure for GM products in Part V.A.2.²¹⁵

209. Greenpeace, Say No to Genetic Engineering, <http://www.greenpeace.org/international/campaigns/genetic-engineering> (last visited March 23, 2007).

210. Gary E. Marchant, *From General Policy to Legal Rule: Aspirations and Limitations of the Precautionary Principle*, 111 ENVTL. HEALTH PERSP. 1799 (2003).

211. See, e.g., Applegate, *supra* note 185; Emily Marden, *Risk and Regulation: U.S. Regulatory Policy on Genetically Modified Food and Agriculture*, 44 B.C. L. REV 733 (2003); Bratspies, *supra* note 13 (exploring the divergence of American and European attitudes regarding GM food products and the impact on consumer confidence).

212. See Applegate, *supra* note 185, at 249–58.

213. Rio Declaration of the United Nations Conference on Env't & Dev. (UNCED), Principle 15, June 14, 1992, 31 I.L.M. 874.

214. See Mandel, *supra* note 187, at 2231–35.

215. See *infra* note 266 and surrounding discussion.

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.

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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

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

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 transgenic 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).

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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.

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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.

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/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>.

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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

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.

304. Moulard, *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>.

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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 FDCA³⁴⁶—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.nwsources.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,

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.

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

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 corn, shared properties with some known food allergens. See Bratspies, *supra* note 13, at 386.

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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 led 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

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

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 organisms⁴²⁵

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 deficiency⁴²⁸ 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

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

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.

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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 increase 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.

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.