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

Part 1

by

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

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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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 debate[4]—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.

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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)) [herinafter 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).

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 2002[5] 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

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]

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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

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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).

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 Unites 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,

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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]

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41. Pure Food and Drug Act of 1906 § 8; s*ee 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; s*ee 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

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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.

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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]

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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 use . . . .[82]

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]

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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

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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]

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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.*

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

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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. § 511.1(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 analsyis 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

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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]

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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 theses 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 pesticides[205] 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.

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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.

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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).

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 heath, 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]

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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.