An Agricultural Law Research Article

Food Products Affected by Biotechnology

by

Robert A. Bohrer

Originally published in UNIVERSITY OF PITTSBURGH LAW REVIEW
55 U. PITT. L. REV. 653 (1994)

FOOD PRODUCTS AFFECTED BY BIOTECHNOLOGY[1]

*Robert A. Bohrer**

INTRODUCTION

From its inception, the development of genetic engineering as a commercial technology has been fraught with controversy over the adequacy of the legal framework for its regulation.[2] The earliest such controversy, debated hotly at the Asilomar meeting,[3] focused on the inherent unpredictability and possible dangers of any new recombinant organism, especially where either the DNA-recipient organism or the DNA-donor organism was a pathogen.[4] With the creation of the NIH-RAC[5] and the passage of time, public anxiety over basic laboratory research has been generally allayed. As research involving the use of genetic engineering progressed beyond the laboratory, however, new controversies were created that rekindled public concern.

Despite the continuing debate over the environmental release of genetically engineered microorganisms[6] and the long-range concerns about the impact of human gene therapy,[7] possibly no application of biotechnology is likely to elicit more public concern than the use of

---

1. This article is based in part on a chapter in the author's forthcoming book on biotechnology law to be published by The Michie Company.

* Professor of Law, California Western School of Law. B.A. 1971, Haverford College; J.D. 1974, University of Illinois College of Law; LL.M. 1979, Harvard Law School.

2. *See* Judith P. Swazey et al., *Risks and Benefits, Rights and Responsibilities: A History of the Recombinant DNA Research Controversy*, 51 S. CAL. L. REV 1019 *passim* (1978).

3. *Id.* recounting the landmark February, 1975, meeting that was held at Asilomar California. The Asilomar meeting has become famous as the beginning of the public oversight (rather than simply a debate among scientists) over recombinant DNA experimentation.

4. *Id.*

5. The Asilomar meeting ultimately resulted in the formation of the National Institutes of Health Recombinant-DNA Advisory Committee (NIH-RAC) and the promulgation of the NIH-RAC Guidelines for Research Involving Recombinant DNA Molecules (the NIH-RAC Guidelines, 52 Fed. Reg. 16,976, May 7, 1986). Compliance with the Guidelines (which have been frequently revised) is mandatory for any research involving recombinant DNA which is conducted at an institution which receives any funds from the NIH.

6. Edward L. Korwek & Peter L. De La Cruz, *Federal Regulation of Environmental Releases of Genetically Manipulated Microorganisms*, 11 RUTGERS COMPUTER & TECH. L.J. 301, 310-14 (1985).

7. *See* Robert A. Bohrer, *Future Fall-out From the Genetic Revolution*, 24 FUTURES 681 (1992).

biotechnology in the production of food products.[8] The first major controversy over the use of biotechnology in food production was the application for permission to market recombinant bovine somatotropin (r-BST) as a new animal drug to increase milk production in dairy cows. This application, approved in November of 1993,[9] was filed in 1987. This extraordinary six-year period of regulatory review and public controversy is strong evidence of the degree of concern raised by the first food products affected by biotechnology. While r-BST is highly controversial and involves a new animal drug, much of the regulation of food biotechnology will center on genetically engineered food crops, such as Calgene's slow-rotting tomato. The FDA has begun to address the food safety issues raised by plant biotechnology through a policy statement published in the Federal Register on May 29, 1992.[10]

The regulatory framework for a food product affected by biotechnology is determined by the purpose for which the biotechnological process has been used. This article provides a general overview of food safety regulation in part II. This article then examines the specific issues of new biotechnology-produced food plants or plant-derived ingredients and the FDA Statement of Policy, (part III), biopesticides used on foods (part IV), new animal drugs (part V), genetically engineered food animals (part VI), and case studies of the Calgene tomato (part VII) and r-BST (part VIII). The conclusion (part IX) reached by an examination of these case studies is that decisionmaking about biotechnology food products has been and will continue to be greatly affected by the qualitative factors which determine public risk perception[11] in this and other areas of technological innovation.

II. THE BASIC REGULATION OF FOOD SAFETY (OTHER THAN PESTICIDES AND VETERINARY THERAPEUTICS)

All food is subject to some form of safety regulation. Even common, longstanding foods such as canned peaches are subject to regula-

---

8. *See* Warren Ausubel, *Federal Regulation of Genetically Engineered Food Additives and Pesticides*, 4 HIGH TECH. L.J. 115 (1989).

9. Robert L. Hotz, *Fruits of Genetic Tinkering Are Headed for U.S. Tables*, L.A. TIMES, Nov. 12, 1993, at A-1.

10. 57 Fed. Reg. 22,984 (1992).

11. As will be more fully detailed in part IX, public risk perception has long been known to be more directly related to factors such as the voluntariness of the risk and the newness of the technology than objective measures of risk such as actual expected mortality rates. *See* note 111 *infra*.

tion for good food manufacturing practice,[12] contamination,[13] and accurate labeling.[14] If a food is of "natural biological origin," was commonly consumed in the United States prior to 1958, and has not been modified by any process which was introduced after 1958, then it is essentially only regulated for manufacturing practices and labeling.[15] By contrast, marketing a food that *has* been modified by a process introduced after 1958 (obviously genetically engineered foods come under this category) may entail more elaborate regulatory review of some kind. Understanding the basic regulation of food safety by the FDA for such "new foods" requires a brief review of three fundamental food safety concepts: adulterated food; food additive; and generally recognized as safe.

A. Adulterated: The First Concept of Food Safety

The Food, Drug and Cosmetic Act[16] provides that adulterated food may not be sold or transported in commerce. Food is adulterated[17] if it bears any added harmful substance other than an approved food additive, an approved residue of a new animal drug, or, on raw foods, a permitted level of pesticide residue.[18] In turn, under section 346, all poisonous or deleterious substances that are added to food[19] are statutorily defined as unsafe except to the extent that their use is required or their presence cannot be avoided despite the use of good manufacturing practices.[20] In the event that an added poisonous substance cannot be avoided, then the agency (the FDA in the case of substances other than pestides, the EPA in the case of pesticides) must set a limit on the

12. 21 C.F.R. § 110.5 (1993).

13. 21 U.S.C. § 342(a)(3) (1988).

14. 21 U.S.C. § 343 (1988 & Supp. IV 1992).

15. 21 C.F.R. § 170.30 (199_). The FDA announced that it will review the otherwise presumptively GRAS status of ingredients of natural biological origin that have been widely used for nutrient properties and that have been significantly altered by breeding and selection or by the manufacturing process.

16. 21 U.S.C. § 342 *et seq.* (1988 & Supp. 1993).

17. 21 U.S.C. § 342 (1988 & Supp. 1993).

18. 21 U.S.C. § 342(a)(2)(A) (1988 & Supp. 1993). "A food shall be deemed to be adulterated . . . if it bears or contains any added poisonous or added deleterious substance (other than one which is (i) a pesticide chemical in or on a raw agricultural commodity; (ii) a food additive; (iii) a color additive; or (iv) a new animal drug) which is unsafe within the meaning of section 346 of this title."

19. Naturally occurring substances, such as molds and fungii, which are known to be harmful, may also result in a food being adulterated. Adulteration by naturally occurring substances or processes is beyond the scope of this article.

20. 21 U.S.C. § 346 (1988).

amount of the substance that can be contained in any food product, at a level necessary to protect human health.[21] Thus, any substance that is not a natural component of a food renders the food adulterated if it may be harmful to human health. If food contains such an added substance that may be harmful to health, it is adulterated unless the added substance is a permitted additive or residue.

Thus, the producer of a food product containing an ingredient, substituent,[22] or added substance faces a fairly straightforward decision-tree, although particular decisions may be difficult to make. If the product is a biopesticide or new animal drug, it can only be used in conformity with the tolerance set for it. If it is an added substance that "may be harmful to health," it can only be used if it is a permitted food additive.[23] The most difficult decision is whether an added substance "may be harmful to health," or creates a reasonable probability of harm. For food plants affected by genetic engineering, that determination is considered in some detail in the FDA Statement of Policy.[24]

B. Food Additive: Added Substances Which Do Not Adulterate

A food additive is any substance that will become a part of or affect the characteristics of any food (other than permitted residues of new animal drugs or pesticides) that is not generally recognized as safe by experts in the field.[25] The purpose of genetically engineering a food

---

21. 21 U.S.C. § 342 (1988).

22. A substituent is the chemical term for the addition of an atom or a group of atoms as a functional group. In the sense used here, genetically engineered changes add a molecule (group of atoms) that becomes part of the altered chemical structure of the resulting plant.

23. A major conflict inherent in this scheme lies in the distinction drawn between pesticide residues on raw foods (such as lettuce or tomatoes) which are subject to the tolerance level regulation discussed in the text and pesticide residues on the processed versions of the same crop, such as canned tomato sauce, which are treated as added substances and therefore subject to food additive regulation as discussed in the text. United States v. Ewig Bros., 502 F.2d 715 (7th Cir. 1974). This conflict is the subject of a recent proposal by the Clinton administration to allow pesticides to be found in processed foods under tolerance levels that would allow minimal risk rather than the zero risk standard of 21 U.S.C. § 342(a)(2) (1988 & Supp. 1993). This very interesting problem will largely affect traditional chemical pesticides rather than biotechnology products and is thus beyond the scope of this article.

24. *Infra*, part III.

25. Section 321 of U.S. Code Title 21 defines food additive as follows:

> (s) The term "food additive" means 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 . . . if such substance is not generally recognized, among experts . . . (through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include . . . [pesticide chemicals and new animal drugs].

plant or food animal would generally be to achieve an effect that is included within the statutory definition of food additive that is, to become a component of the food or to otherwise affect its characteristics.[26]

In the case of genetically engineered food products, the added substance is the genetic material and the resultant protein (or in some cases, the resulting changed level of protein, or changed product of a protein-regulated metabolic pathway). Thus, the result of genetically engineering a food plant or food animal would appear to be one of three statutory alternatives: either the resulting food is adulterated; the gene or its resulting product are the subject of a food additive regulation permitting and prescribing its use: or, the product is neither adulterated nor the subject of a food additive regulation because the gene and its resulting product are safe or generally recognized as safe.

C. *Generally Recognized as Safe: Between Additive and Adulteration*

The concept of generally recognized as safe, GRAS (by experts qualified by scientific training and experience to evaluate the safety of food additives),[27] is the final basic concept in food safety regulation. A food is not adulterated, despite containing an added substance not subject to a food additive regulation, if the added substance is GRAS.[28] Under the regulations, GRAS status can be achieved in one of two ways, both of which are arguably relevant to food biotechnology.

The first route to GRAS status may be that a substance was commonly consumed in the United States prior to January 1, 1958.[29] For example, if one were to engineer a food plant (e.g. corn) to contain a protein usually found in another plant food that was commonly consumed prior to 1958 (e.g. soybeans), the resulting food product may fall within this first category of GRAS. While corn containing soy-protein did not exist prior to 1958, the soy protein gene and its related protein were commonly consumed in food prior to 1958. This common consumption experience must still be of the sort that would be accepted by experts as establishing the safety of the food additive, but it may obviate the need for independent, controlled studies of the food additive. Thus, if experts would agree that the soy protein must be safe

21 U.S.C. § 321(s)(1), (2), (5) (1972).

26. 21 U.S.C. § 321 (1988).

27. *See* 21 C.F.R. § 170.30 (1993).

28. *Id.*

29. *Id.*

because of its widespread consumption prior to 1958, the engineered corn containing soy protein gene and soy protein should be GRAS.

The other route to GRAS status is through complete and thorough scientific studies of the proposed food ingredient and the resulting food product.[30] For obvious reasons, this route to GRAS is considerably more expensive, and therefore less desirable, than basing GRAS status on widespread consumption prior to 1958. The scientific studies required for food additives, incorporated by reference into the GRAS process, "should include detailed data derived from appropriate animal and other biological experiments. . . ."[31] Nevertheless, for some biotech food products, this alternative may be the only route to market approval other than a full-scale petition for a new food additive regulation. If one were to engineer a novel enzyme into corn to produce a low-calorie corn oil, it is likely that the resultant food product would need to gain GRAS status through scientific studies of the toxicology of the oil in mammals (or the enzyme and resulting oil would need to be approved by the food additive petition process).

If the studies required for GRAS status (other than for a substance commonly consumed before 1958) are in many ways the equivalent of those required for a food additive petition, what are the advantages of seeking GRAS status rather than submitting a food additive petition? There are three reasons why GRAS status is preferable. First, GRAS is self-executing. Although the FDA has adopted the principle that GRAS determinations require rigorous testing and publication of studies, the sponsor of an ingredient is the one who will decide whether the studies justify the conclusion that the substance is GRAS.[32] Second, GRAS determinations are generally broader than the very narrow uses permitted for food additives (and subsequent expanded uses of GRAS substances are more easily obtained). Third, where the sponsor of an ingredient seeks FDA affirmation of its GRAS

---

30. 21 C.F.R. § 170.30(h) (1993).

General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient. General recognition of safety through scientific procedures shall ordinarily be based upon published studies which may be corroborated by unpublished unpublished studies and other data and information.

31. 21 C.F.R. § 171.1(c)(E) (1993).

32. Cyclamate, a widely used non-nutritive sweetener, was the subject of one of the more widely publicized instances in which a substance was marketed as GRAS and then, after FDA review, pulled from the market as an unapproved additive. *See* Michael E. Taylor, *Food Safety Regulation*, in FOOD AND DRUG LAW 182, 198-200 (Richard M. Cooper ed., 1991).

status, the FDA review process itself is likely to be quicker and less cumbersome. The regulatorily created affirmation procedure is most often used for pre-1958 food substances altered by a process developed since 1958,[33] a category that, in the future, may well include a great many genetically engineered foods.

Under the FDA's Statement of Policy for New Varieties of Food Plants,[34] the self-determinations of GRAS or, in some cases, GRAS affirmation, will be the desired path for any biotech product that can qualify for such treatment. This self-determination that an added substance is clearly not one that "may be harmful to human health" requires no regulatory premarket review whatsoever, although the producer who introduces such a product without asking the FDA to affirm its GRAS determination does so at its own peril.

III. New Food Plant Varieties Created by Genetic Engineering—The FDA Statement of Policy[35]

Many applications of genetic engineering to food plants will be intended to affect the taste, quality, or growing characteristics of the plant (other than for pest-resistance) and, as discussed in the preceding section, may be covered either as a food additive or conversely as an adulterant under the FDCA.[36] The FDA Statement concerning such new varieties of food plants is an important effort by the agency to clarify the rules under which such products will be regulated. The FDA Statement provides an analytic framework for genetically engineered food plants that contains three possible outcomes: "no concern"; "consult FDA" (which includes both the possibility of informal regulatory approval as well as the requirement for formal GRAS affirmation or food additive review); and, "new variety not acceptable."[37]

The basic positions taken in the FDA Statement are simple. First, genetically engineered food plants will not be subjected to a per se requirement of special labeling, rather, any labeling requirements will depend on the nature of the genetic engineering.[38] Second, the FDA

33. See O'Reilly, Food and Drug Administration 11-17 (1991).

34. 57 Fed. Reg. 22,984 (1992) [hereinafter "FDA Statement"].

35. *Id.*

36. Food, Drug and Cosmetic Act, 21 U.S.C. § 348 (1988).

37. FDA Statement, *supra* note 34, at 22,992.

38. This is the position taken in the FDA Statement as originally published in May of 1992. The change in administrations from Bush to Clinton has been accompanied by a notice from the FDA that the issue of labeling is being reconsidered. See 58 Fed. Reg. 25,837 (1993) (requesting comments on a variety of issues related to the question of whether some of all genetically engi-

Statement provides that nucleic acid sequences, or genes themselves, when introduced into plants to produce an effect, are presumed to be safe.[39] Thus, the FDA will be looking at the nucleic acid sequences' effects on the composition of the food product rather than at the DNA itself. With respect to the effects on composition, the FDA outlined its position on four major categories of possible effects: alteration of protein levels of proteins native to the plant; introduction of a protein not native to the plant; changes in carbohydrates or introduction of new carbohydrates; and, changes in or introduction of new fat or oil constituents of the plant. Each of these can be separately summarized.

A. Alteration of the levels of a protein native to the plant

Some efforts at genetically engineering food plants may be thought of as intra-generic; that is, the desired end is to increase or decrease the production of a particular protein native to the plant, rather than the introduction of a new gene sequence—not previously found in this species—to produce a new plant constituent. An example of this kind of intra-generic genetic engineering is the effort by Calgene to use an "anti-sense" nucleic acid sequence to inhibit the production of the to-

---

neered foods should be distinctly labeled as such).

The labeling controversy is an unfortunate example of the complex interaction between public perception and regulation. The purpose of labeling would appear to the author to be to provide consumers with sufficient information upon which to make an informed choice. This would not be accomplished by any per se requirement that food products from genetically engineered plants bear a required label indicating that genetic engineering was used in producing the plant variety. For example, the public would not be able to use such a per se label to discriminate between plants in which genetic engineering had been used to lower the levels of saturated fat (arguably yielding a healthier food) and plants in which genetic engineering had been used to add bacillus thuringensis endotoxin to improve the plants' pest-resistance. If all arguably relevant information is provided in some summary fashion (i.e. the function of the nucleic acid sequences introduced into the plant, the percentage changes in composition of the major constituents of the plant, and some assessment of the significance of those changes in composition still other problems arise. First, such information is likely to be both overwhelming and poorly understood. Second, unless similar requirements are imposed on "naturally" produced new food plant strains, the result will not be to enable a reasoned choice but to increase the likelihood of an unreasoned choice of unlabelled products rather than labelled products.

39. "Nucleic acids are present in the cells of every living organism . . . and do not raise a safety concern as a component of food. In regulatory terms, such material is presumed to be GRAS." 57 Fed. Reg. 22,984 at 22,990 (1992). The scientific basis for this is simply that the DNA in all foods is comprised of precisely the same chemical (although of course in varying nucleotide sequences) and is always broken down in the digestive process. In other words, although to the living organism DNA sequences make all the difference in the world, to the consumer DNA is DNA.

mato enzyme that causes the tomato to rot.[40] Thus, Calgene used "antisense" genetic engineering to control the levels of substances ordinarily found in that edible plant species. In general, where the effect of genetic engineering is to alter the percentage composition of proteins native to that plant, the FDA's concerns are whether or not such changes may have an affect on toxicants present in that species and whether or not the result is a significant change in the nutritive value of that food.[41] In the case of intra-generic, genetically engineered plants, where there is no resulting increase in toxicant levels[42] or the overall nutritive value of the food, the FDA's position is one of "no concern."[43]

B. Introduction of a protein not native to the plant (inter-generic genetic engineering)

A variety of desirable characteristics may be transferred to a plant from another plant species, or even from a bacterial or animal species. For example, gene sequences encoding proteins conferring drought-tolerance, ordinarily found in a desert plant species, might be engineered into a variety of domestic wheat. For such "inter-generic" genetically engineered food plants, the Statement again quite properly looks to the characteristics of the introduced protein to guide the regulatory process. If the protein will be found in foods produced from the plant and is not one with a history of safe use in food (as may well be the case with the hypothetical desert plant "drought proteins"), then the principal questions raised by the FDA focus on the effect of the new protein on levels of any toxicants native to the engineered plant and the allergenicity and toxicity of the introduced protein.[44]

---

40. The strand of the double-stranded DNA that is transcribed into RNA and then translated into an amino acid chain or protein is referred to as the 'sense" strand. The complementary strand that binds to the sense strand, and while bound to it prevents transcription, is referred to as the "antisense" strand. By inserting the complementary sequence or antisense sequence for a target gene (the 'rotting" enzyme gene) into the sense strand of the tomato's DNA, this 'antisense" DNA will be transcribed into RNA along with the 'sense" DNA. When its antisense RNA binds to the complementary sense RNA, translation into protein is blocked. For a discussion of the Calgene approach see Carl T. Hall, *Calgene Gets Patent for Miracle Crops*, S.F. CHRON., Apr. 23, 1992, at B1.

41. *See* FDA Statement, *supra* note 34, at 22,993 (Figure 1).

42. Any increase in the levels of a toxicant would require the producer of a food product to consult with the FDA.

43. FDA Statement, *supra* note 34, at 22,995 (Figure 2). "Safety Assessment of New Varieties: The Host Plant." The particular issues raised by the Calgene tomato will be discussed in greater detail in part VII of this article.

44. FDA Statement, *supra* note 34, at 22,999-23,000.

In many cases, the question of allergenicity and toxicity will be determined from the similarity of the introduced protein to other proteins, its biological function, and any reports of its toxicity. What is most significant is the FDA's initial position that, with the exception of a limited list of known allergenic proteins[45] and an even more limited list of known toxic proteins with enzymatic function,[46] introduction of new proteins into food crops does not automatically require Agency review of a manufacturer's food safety data. Instead, the Statement allows the producers of such foods to determine independently the safety of the resulting food.[47] In regulatory terms, although the introduced protein is clearly an "added substance," the producer of the genetically engineered food may make its own determination that the food is not one that "may be harmful to human health" and therefore is "generally recognized as safe."[48] Thus, the FDA will not require a premarket review of all inter-generic genetically-engineered food plants, even those containing proteins not previously found in foods (in statutory terms, without a "history of safe use in food").[49] Of course, if a producer of such a food is wrong and the protein turns out to be allergenic or toxic, the FDA can seize the food as adulterated.[50] There is also the potential for enormous civil liability.[51]

In most cases intergeneric genetically engineered plants producing

---

45. FDA Statement, *supra* note 34, at nn.19-20. The FDA Statement asks manufacturers to discuss allergenicity testing or labelling where a gene is used to transfer a protein from a food which is known to be allergenic to a food which is not known to be allergenic, using the example of the transfer of a nut protein (nuts are common allergen) to corn (not an allergen).

46. See FDA Statement, *supra* note 34, at n.15 (Figure 4). The flowchart of Figure 4 has three routes which lead to "Consult FDA": allergenic donor; toxic protein; and "likely to be a macroconstituent in the human or animal diet."

47. That is, to determine toxicity, effects on host plant toxicant levels, and, to the extent possible, the potential for allergenicity. As to this latter point, the FDA Statement concludes that no routine procedures for determining allergenicity currently exist. FDA Statement, *supra* note 34, at 23,000 n.6.

48. The FDA Statement Figure 4 takes the position that these are matters that raise "No concerns" for the Agency and thus are left to the manufacturer's determination.

49. FDA Statement Figure 4 summarizes the FDA's position that although a protein does not come from a food source and is not similar to an edible protein, "no concerns" are raised so long as the biological function of the protein does not raise any safety concern, the protein is not reported to be toxic, and the protein is not likely to be a macroconstituent of the diet.

50. FDA Statement, *supra* note 34, at 22,989.

51. Although it is speculative to predict the theory of liability which courts will impose on producers of genetically engineered foods that cause injuries, it is likely that such foods will be analyzed as defective and unreasonably dangerous products under the commonly used "consumer expectation" test. *See, e.g.*, Yong Cha Hong v. Marriott Corporation, 656 F. Supp. 445 (Md. 1987); *compare* Mexicali Rose v. Superior Court, 4 Cal. Rptr. 2d 145, 822 P.2d 1292 (Cal. 1992).

novel proteins will not undergo pre-market review by the FDA because it is unlikely that any producer of genetically engineered food plants would choose to introduce a protein known to be toxic or allergenic, or even one similar to known toxic or allergenic proteins. For a protein without a history of safe use in food that is likely to be a "macroconstituent" in the human (or animal) diet, however, the FDA will require pre-market consultation, if not approval, even where the protein is not from a donor species commonly allergenic, is not reported to be toxic, and is of the type of protein ordinarily well-digested in humans.[52] The basis for this requirement is unclear, because the Statement itself concludes "from a nutritional standpoint, the amount and quality of total protein in the diet, rather than of any particular protein, is of greatest significance."[53] Nevertheless, the Statement clearly distinguishes between proteins likely to be "consumed at a substantial level" and states that "[d]ietary exposure to such proteins should be considered."[54] This is a substantial departure from the traditional approach to food additive safety, which does not exempt additives from pre-market review simply because they will be used in only a few foods or in trace amounts.[55] While it is doubtless true that the less exposure, the less the resulting harm, the Statement's use of the concept of dietary "macroconstituent" has no apparent basis in the statute and may well be a focus for criticism of the FDA's policy or even a challenge by a consumer food safety group.[56]

---

52. FDA Statement, *supra* note 34, at n.6 (Figure 4).

53. *Id.* at n.16.

54. *Id.*

55. E.g. Aflatoxin, which is limited to concentrations measured in parts per billion. 39 Fed. Reg. 42,748 (1974).

56. It is the author's opinion that industry self-policing, whether motivated in part by the fear of liability, is likely to prevent any toxic proteins from being introduced into genetically engineered crops. The problem of allergenicity, however, is a much more difficult one. Although allergenic proteins may share some common structural features, it is currently difficult to determine, on the basis of any laboratory tests or even limited human trials, whether a particular protein, newly available for human consumption, will prove allergenic in a very small percentage of the population. Thus as a practical matter, the FDA's apparent acceptance of the possibility that novel proteins may be allergenic is an acceptance of the current state of the art for food additives and food safety generally. Consequently, genetically engineered recombinant proteins are being treated like traditional food ingredients: the potential for rare allergenicity is simply ignored. This may be sound public policy, but any potential incident involving even a few severe allergic reactions to a genetically engineered food is likely to produce enormous public concern. See part IX, *infra*.

C. *Changes in Carbohydrates or Introduction of New Carbohydrates*

While DNA itself only encodes proteins, many proteins have enzymatic or metabolic functions; that is, they operate on other substances to produce carbohydrates or lipids (fats and oils), the other major categories of molecules found in plants and animals. Thus, one of the results of genetically engineering a food plant can be to affect a metabolic pathway, resulting in a change in a carbohydrate or lipid produced by the engineered organism.[57] Plant varieties might be engineered to contain new or modified carbohydrates because of the characteristics those carbohydrates contribute to the food or, in some cases, the new or modified carbohydrate might be extracted to be used as an ingredient in other foods.

In the case of such carbohydrates, the Statement raises only two questions: does the resulting carbohydrate contain any structural features not ordinarily found on food carbohydrates, and, if the carbohydrate is likely to be a macroconstituent of the diet, are there any changes that are likely to affect digestibility or nutritional qualities?[58] Although the two questions present a relatively simple decision tree, the net result may well be that new carbohydrates are treated more stringently than new proteins. There may be several reasons for that greater scrutiny. First, proteins are, with few exceptions, broken down quickly in the digestive tract into small polypeptides or amino acid chains, regardless of their amino acid sequence or three-dimensional folded structure.[59] On the other hand, some complex carbohydrates with unusual functional groups are not so quickly broken down, and, in fact some complex carbohydrate polysaccharides are toxins. The properties of a complex carbohydrate containing an unusual structural feature or functional group would be difficult to predict. Small changes in simpler, readily-digested carbohydrates (for instance to enhance sweetness) are likely to fall into the "no concerns" category, and thus allow the producer to make its own determination that the substance is safe and escape premarket review. Thus, a slightly altered, novel, ge-

57. FDA Statement, *supra* note 34 (Figures 5 and 6).

58. FDA Statement, *supra* note 34, at 23,001 (Figure 4).

59. "FDA has historically considered proteins, as a class of chemical food additives, to be of relatively low concern . . . . Additionally, it is important to remember that proteins are digested by proteases present in the saliva, stomach and duodenum." K. Redenbaugh et al., *Regulatory Issues for Commercialization of Tomatoes with an Antisense Polygalacturones Gene*, 29 IN VITRO CELL. DEV. BIOL. 17, at 22 (1993) *citing Toxicological Principles for Safety Assessments of Direct Food Additives and Color Additives Used in Food* (FDA, BUREAU OF FOODS 1982).

netically engineered carbohydrate that has no unusual structural groups and is of the same digestibility and nutritional value as common food carbohydrates could avoid FDA premarket review.

D. New or modified fats or oils (lipids)

The Statement provides a slightly different regulatory scheme for fats or oils from the one described above for new or modified carbohydrates. Again, the two questions raised in determining whether or not FDA consultation or pre-market review may be required are only slightly different from the questions raised for carbohydrates. For lipids, the first question raised is whether or not the resulting fat or oil will be a macroconstituent of the diet.[60] Consultation is required for such macroconstituents regardless of whether or not there are changes in digestibility or nutritional value. Second, rather than raising the issue of "structural features or functional groups," the Statement asks simply whether the fatty acids produced in the new variety are unusual or toxic.[61] If the new or modified lipid is not unusual or toxic and will not be a macroconstituent of the diet, then the producer can again make its own determination of safety and escape pre-market review.

E. A Brief Overview of the FDA Statement

Since the FDA Statement was first published in 1992, no genetically engineered food plant has yet been released to the market. Nevertheless, it is clear that the Statement of Policy answers several important questions about the regulation of biotechnology-derived foods. First, as in other areas[62] these products of biotechnology will be regulated within the statutory and regulatory frameworks which had been established prior to the development of recombinant DNA technology. Second, the FDA Statement emphasizes the principle that genetic engineering is a method, and that regulation of food is aimed at the product, not the method by which the crop strain was originally derived. Third, genetic engineering will, in general, result in more precisely understood and controlled changes in the derived crops, as compared with older methods of plant hybridization and crossing. Nevertheless, though the FDA Statement is largely convincing from a scientific and

60. *See* FDA Statement, *supra* note 34, (Figure 6).

61. *Id.*

62. *See* Office of Science and Technology Policy, *Coordinated Framework for the Regulation of Biotechnology*, 51 Fed. Reg. 23,302 (1986).

food safety perspective, it will still fail to satisfy consumer advocates whose concerns stem largely from a lay, qualitative risk perception of the risks of genetic engineering.[63] We are likely eventually to see mounting public pressure on the Congress and the FDA that will result in more regulatory oversight than the FDA statement would now impose.

IV. Food Plants Engineered to Produce a Biopesticide or Treated With a Biotechnology Derived Biopesticide

One application of biotechnology to food plants is likely to be the introduction of pest-resistance characteristics. Several companies have been experimenting with the creation of "transgenic" plants[64] using the gene encoding the biopesticide bacillus thuringensis endotoxin (b-t toxin, effective against lepidopteran insects). In a very recent plant research breakthrough, scientists at Scripps Research Institute announced the cloning and successful expression of a gene conferring resistance to a common plant virus.[65] The gene used was an altered form of the gene encoding the protein that the virus uses to enter plant cells, and blocked the virus from entering the plant cells. The original experiment was done in tobacco, but the approach promises broad potential applicability in a wide range of food crops. In some cases, rather than attempting to build into a food plant the gene to produce a useful protein, it may be worthwhile simply to spray the growing plant either with the protein itself or with a microorganism that produces the protein. For example, lettuce may be sprayed with the b-t toxin or with a microorganism that produces the toxin. (Ordinary bacillus thuringensis, the source organism for b-t toxin and its gene, is too short-lived when exposed to sun and weather to be useful for this purpose.)

Food plants that have been genetically altered to resist pests or disease, or that have been treated with genetically engineered biopesticides or biological control agents, will be regulated by the EPA under FIFRA.[66] EPA will also have jurisdiction over the food safety issues of those plants under the FDCA.[67] The FIFRA definition of pesticide is

63. *See infra* part IX (discussion of risk perception).

64. Transgenic plants are those in which genetic material derived from another species has been inserted by genetic engineering.

65. David Graham & Drew Silvern, *Added Gene May Boost Crop Yields*, San Diego Union Trib., Dec. 12, 1993, ed. at B1, Col. 6.

66. 7 U.S.C. § 136 (1991).

67. *See* 21 C.F.R. § 109.6 (1993).

broad enough to cover all pest-control agricultural uses of biotechnology.[68] To use the example of the Scripps viral gene approach, the gene and the encoded protein would be the active ingredient. The resulting plant may be considered a biological control agent under FIFRA,[69] and would first be examined from an environmental safety perspective for market approval.[70]

If a genetically engineered, virus-resistant food plant is determined not to threaten unreasonably adverse environmental effects, the next issue would be the food safety question. For pesticides that will be detectable in food products (and in our example, the viral-resistance gene and its protein are arguably detectable residues), the food safety regulatory problem is one of setting a tolerance level (determining the residual level which is acceptable). Pesticide tolerances on raw foods, below which level the presence of the pesticide substance does not constitute adulteration, are to be set at a level "necessary to protect the public health. . . . [G]iving appropriate consideration, among other relevant factors, *(1) to the necessity for the production of an adequate, wholesome, and economical food supply*; [emphasis added]."[71] Further, under the so-called "pass-through" provisions of § 342(a) of the FDCA, the same tolerance level applies if the raw food containing the pesticide residue becomes an ingredient in a processed food, for example a tomato in tomato sauce, or on a frozen pizza. The raw food tolerance standard, which expressly mandates consideration of economic benefits as well as health costs, is significantly less stringent than the standard for general food additives. For food additives, any reliable evi-

---

68. 7 U.S.C. § 136(u) (1991). The term "pesticide" means (1) any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, and (2) any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant [except] . . . any article that is a "new animal drug."

69. Definitions, 40 C.F.R. § 152.3 (1992).

(b) *Active ingredient* means any substance (or group of structurally similar substances if specified by the Agency) that will prevent, destroy, repel or mitigate any pest, or that functions as a plant regulator, desiccant, or defoliant within the meaning of FIFRA sec. 2(a).

(i) *Biological control agent* means any living organism applied to or introduced into the environment that is intended to function as a pesticide against another organism declared to be a pest by the Administrator.

70. 7 U.S.C. § 136a(c)(5) (1976).

The Approval of Registration Administrator shall register a pesticide if he Administrator determines that . . .

(c) it will perform its intended function without unreasonable adverse function without unreasonable adverse effects on the environment. . . .

71. 21 U.S.C. § 346a(b) (1972).

dence of carcinogenicity bars the use of the additive under the often-criticized Delaney clause.[72]

At the time this article was written, the pesticide tolerance statutes and regulations are being subjected to intense debate, in part as a result of the decision in *Les v. Reilly*.[73] In *Les*, the Ninth Circuit held that where pesticide residues in processed foods exceed the levels permitted under the tolerance set for the pesticide in raw foods (and thus exceed the "pass-through" levels), the strict food additive standards, including the "zero risk" standard of the Delaney clause,[74] apply to the pesticide in the processed food.[75] Although the *Les* decision does not immediately or directly affect the use of genetic engineering to create pest resistant food plants or genetically-engineered biopesticides, it may prompt significant statutory changes that would affect all pesticide regulation.

V. New Animal Drugs and Biologics Used to Treat Food Animals

Some agricultural biotechnology products will be classified as new animal drugs and will be regulated by the FDA under the FFDCA[76] or regulated as new animal biologics by the USDA under the Virus-Serum-Toxin Act.[77] Where a new veterinary product is derived from a virus, serum, toxin, or analogous substance of natural or synthetic origin and achieves its intended affect largely by immunological means, it is likely to be classified as a biological.[78] If it is intended to affect a structure or function of a non-diseased animal, then it is likely to be classed as a drug.[79] As in the case of r-BST,[80] there may be an overlap between the USDA and the FDA arising from this somewhat vague distinction between new animal drugs and animal biologics that will

---

72. 21 U.S.C. § 348(c)(3)(A) (1972).

Provided, That no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal. . . .

73. 968 F.2d 985 (9th Cir. 1992).

74. 21 U.S.C. § 348(c)(3)(A) (1988).

75. *Les*, 968 F.2d at 989.

76. 21 U.S.C. §§ 321, 360b (1972 & Supp. 1993).

77. 21 U.S.C. §§ 151-159 (1972 & Supp. 1993).

78. 9 C.F.R. § 101.2(w) (1993).

79. For an overview of the distinction between new animal drugs and biologics see Daniel D. Jones, *Genetic Engineering in Domestic Food Animals: Legal and Regulatory Considerations*, 38 Food Drug Cosm. L.J. 273, 284-85 (1983).

80. *See infra* part VIII.

require an agreement between the FDA and USDA as to jurisdiction. The FDA's approval of a new animal drug involves three basic criteria: safe for the animal; safe for humans (exposed via consumption or otherwise); and, effective.[81] Thus, once a new animal drug is tested and the data is submitted to the FDA (or, for an animal biologic, the USDA), the process for food safety approval is very similar to that for approving a pesticide. If the use of the new animal drug or biological will result in it being found in food derived from treated animals, the data submitted must include a proposed tolerance level.[82] If the proposed new drug is carcinogenic, it cannot be approved if any detectible residue will remain in any edible portion of the animal.[83]

---

81. 21 U.S.C. § 321 (1988 & Supp. IV 1992):

(u) The term "safe," as used in paragraph (s) of this section and in sections 348, 360b and 379e of this title, has reference to the health of man or animal. . . .

(w) The term "new animal drug" means any drug intended for use for animals other than man, including any drug intended for use in animal feed but not including such animal feed,—

(1) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof; except that such a drug not so recognized shall not be deemed to be a "new animal drug" if at any time prior to June 25, 1938, it was subject to the Food and Drug Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

82. Refusal to approve an application (1993). 21 C.F.R. § 514.111:

(a)(6) Failure to include an appropriate proposed tolerance for residues in edible products derived from animals or a withdrawal period or other restrictions for use of such drug if any tolerance or withdrawal period or other restrictions for use are required in order to assure that the edible products derived from animals treated with such drug will be safe.

83. 21 U.S.C. § 360b(d)(1)(I) (1988):

[S]uch drug induces cancer when ingested by man or animal or, after tests which are appropriate for the evaluation of the safety of such drug, induces cancer in man or animal, except that the foregoing provisions of this subparagraph shall not apply with respect to such drug if the Secretary finds that, under the conditions of use specified in proposed labeling and reasonably certain to be followed in practice (i) such drug will not adversely affect the animals for which it is intended, and (ii) no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (c), (d), and (h) of this section), in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals;

VI. GENETICALLY ENGINEERED AND TRANSGENIC ANIMALS

The use of recombinant DNA technology in animals, just as in plants, can lead to intra-generic and inter-generic (transgenic) combinations. An intra-generic experiment might seek to alter the characteristics of the animal by inserting an extra copy of a gene which is native to the species (an additional growth hormone gene, for example), while an intergeneric combination might introduce a gene from another species in an attempt to transfer a desired characteristic (such as disease resistance) from one species into another. Two possibilities exist; either the new gene and its product will be considered a new animal drug, or the gene and its product will be considered a food additive. Dr. Daniel Jones has stated that the appropriate classification is as a new animal drug, rather than as an additive.[84] While it is true that the definition of drug is very broad and could well cover the use of recombinant technology to create the first generation transgenic animal, it would be difficult to stretch the definition to conclude that the naturally produced progeny of two "novel" hybrid animals are being treated with a drug. At the same time, it may well be possible to conclude that the offspring are the result of the use of a "substance the intended use of which results . . . directly or indirectly, in its . . . affecting the characteristics of any food. . . ."[85]

It is possible that the regulatory treatment will parallel that described above for genetically engineered plants. Thus, if the new animal contains a protein not ordinarily found in a food animal, the producer and the FDA would have to determine the safety of the protein product. By contrast, if the result of the genetic engineering is merely an alteration of the levels of expression of proteins ordinarily found in food animals, then the protein product is probably not an additive and the gene sequences responsible for the desired characteristics will undoubtedly be GRAS.

VIII. THE CALGENE TOMATO: AN EXAMPLE OF FOOD SAFETY REGULATION FOR GENETICALLY ENGINEERED PLANTS

Calgene, one of the larger companies dedicated to the agricultural uses of biotechnology, has requested that the FDA issue an advisory

---

84. Jones, *supra* note 79, at 284-285.

85. Section 321(5) of the U.S. Code title 21 defines food additive as, "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. . . ."

opinion that its genetically-engineered slow-rotting tomato is a whole food containing no additives.[86] If Calgene's request is approved, it will clarify the regulatory issues involved in at least one major area of food biotechnology, namely, the large number of the potential genetically engineered food crops and food animals in which anti-sense nucleotide sequences are used to inhibit or reduce the levels of one of the plants or animal's normal constituents. Calgene's tomato is produced by adding a non-coding, "anti-sense" sequence for the gene that ordinarily produces the enzyme responsible for degrading the cell walls of ripened tomatoes (i.e. "rotting").[87] Calgene's anti-sense sequence slows the rate of expression of the "rotting" enzyme polyglacturonase (PG). PG is the plant enzyme that causes pectin to degrade, an essential step in the softening, or breakdown, of ripe fruit. By blocking the production of PG, a ripe tomato will stay ripe but firm for a considerably longer period of time, sufficient to allow tomatoes to be picked ripe and still reach the consumer without rotting.[88] Long a focus of consumer complaints, the now ubiquitous supermarket tomato is picked green and artificially "ripened" by exposure to ethylene gas. The difference in taste between vine-ripened and gas-ripened tomatoes is significant.[89]

Calgene's argument with respect to its anti-sense nucleic acid manipulation to slow down rotting is that its tomato contains no additional substance whatsoever (other than non-coding DNA, which is undoubtedly GRAS) and differs from ordinary tomatoes only in the level of the rotting enzyme and the rate of rotting.[90] Calgene thus hopes to have the FDA treat its tomato as it would any other new variety of tomato marketed for its better taste or other desirable characteristics; that is, by not regulating it at all.

Regulatory review of Calgene's anti-PG tomato is complicated somewhat by the fact that Calgene used a common research tool, the gene for kanamycin resistance (the gene "kan(r)"), in order to help select those tomato cells that had been effectively transformed.[91] Linking the anti-PG DNA to the kan(r) gene allows Calgene to select out

---

86. *See* FDA Statement, *supra* note 34, at 22,985.

87. *See supra* note 40.

88. *Are tomatoes with antisense genes food? Calgene requests FDA opinion*, BIOTECHNOLOGY NEWSWATCH, Aug. 19, 1991, vol. 11, no. 16, at 1.

89. Redenbaugh et al., *supra* note 59, at Table 1, p. 18.

90. *Id. See also supra* note 38.

91. Donna K. H. Walters, *FDA Asked to Review Biotech Tomato; Genetic Engineering: The California Company's Request Is The First For An Altered Food Product*, L.A. TIMES, Aug. 13, 1991, at Part D, Page 2, Column 4.

those cells that have been successfully transformed because tomato cells are naturally vulnerable to the antibiotic kanamycin. Only the transformed cells that have taken up and are expressing the kan(r) DNA (and presumably the anti-PG DNA as well) will survive exposure to the antibiotic. The successfully transformed cells are used to propagate new plants that carry the new genes and can propagate the new characteristics (slow-rotting and kanamycin resistance) by seed. Thus, regulatory review of the Calgene tomato requires consideration of two sets of issues: the anti-PG gene and its effect; and, the kan(r) gene and its effect.

All of the food that we eat contains DNA. There can be no question that the DNA itself has no effect on human health and is digested without incorporation and expression by any human cells. In and of itself, an anti-sense sequence of DNA is like any other DNA contained in all of the food we eat, that is, generally recognized as safe (GRAS).[92] The FDA's Statement makes it clear that the real issue for the anti-PG tomato is not the DNA itself, nor the lower level of PG itself (what you do not eat, in general, cannot harm you), but whether the reduced level of PG results in increases in the levels of any other substances that should cause concern.[93] The intended effect of the reduction in PG is a slower rate of breakdown of pectin, which again is of no concern since the resulting level of pectin is not increased beyond that found in vine-ripened tomatoes. Calgene's burden then is a straightforward one; to demonstrate that the effects of PG reduction are limited to the slower breakdown of pectin. Most enzymes, such as PG, are fairly specific in the substances upon which they act, and thus it is not likely that blocking the production of PG has any effect on the levels of any plant proteins other than pectin.

In general then, food products containing anti-sense DNA would appear to be one of the best cases for regulatory clearance of biotechnology food products. The anti-sense DNA sequences ought to be considered GRAS (under the common consumption prior to 1958 standard) and the *reduction* in the target protein level would not appear to cause a problem in most cases (the principal exception being the diminution of an enzyme responsible for the breakdown of a natural plant toxicant). In addition, if as suggested, the reduced level of poly-

92. *See supra* note 25.

93. The FDA Statement at 18 discusses the possibility that an unintended effect of the introduction of a gene sequence may result in the increased production of toxicants by other metabolic pathways in the plant.

galactonurase has no other significant effect beyond preserving a "just-ripe" level of pectin, there is no other basis for regulation. Thus, with respect to the actual slow-rotting property of the tomato, Calgene would appear to have a strong case for regulating the tomato as a whole food containing no additives. The FDA Statement clearly leads to that result, which would be reached under any reasonable reading of the statutes and regulations.

As noted above, Calgene also used a common research tool, the kan(r) gene to facilitate the selection of plants which have been successfully transformed with the desired trait (anti-PG). Unlike the antisense DNA for PG, however, the kan(r) gene does code for the production of a protein, specifically an enzyme (kanamycin phosphotransferase II) that breaks down kanamycin and thus confers resistance to it. The kanamycin resistance enzyme, although common in some species of bacteria, does not generally occur in food plants and animals, and thus its addition to the tomato does present more complicated issues than an anti-sense DNA sequence (or a "sense" or promoter sequence for a protein that *does* commonly occur in food plants or animals). Here the argument for treating the kan(r) enzyme as GRAS becomes somewhat more complex. For this reason, in April of 1991, Calgene took the step of requesting an advisory opinion from the FDA on the safety of using the kan(r) gene in food plants for both human health and the environment. In turn, the FDA published notice of Calgene's request in the Federal Register, and requested public comment.[94]

Using the analytic framework provided in the FDA Statement further underscores the difficulty of the issues raised by using the kan(r) gene as a marker in food biotechnology. Using the flowchart in that document addressed to the problem of newly introduced proteins,[95] two questions in the decision-tree would seem particularly troublesome with respect to kan(r). The first question is whether the biological function of the protein raises any safety concern (or whether the protein is reported to be toxic). Among the evidence that will certainly be relevant to answering this question is the fact that the gene is found in some of the varieties of bacteria to which humans are ubiquitously exposed, including strains of e-coli that are commonly found in the human gut.[96]

---

94. *See* 56 Fed. Reg. 20,004-01 (1991).

95. FDA Statement, *supra* note 34, at 22,999.

96. Calgene also relies on human clinical tests involving the kanamycin resistance protein, *Calgene Forces FDA Hand on Biotech*, SACRAMENTO BEE, Nov. 28, 1990, vol. 268, No. 1380, at

Thus, while there is no apparent basis for believing the protein to be toxic, its effect on the widely used, orally ingested kannamycin-neomycin family of antiobiotics does raise some safety concerns. Although it is highly unlikely that enough of the enzyme would survive the initial stages of the digestive process to affect even a simultaneously administered oral antibiotic, it is not the sort of question that should be answered without at least some data on the amounts of the enzyme that would be ingested, the potency of the enzyme, and its metabolism. While Calgene has undoubtedly done such calculations,[97] the FDA Statement may not have required it to do so.

The second particularly relevant question from the FDA Statement is the question as to whether the introduced protein is likely to be a "macroconstituent in the human diet."[98] As noted in the discussion of the FDA Statement in part III of this article, the focus on the concept of "macroconstituent" is of unclear statutory or regulatory origin, and applying the concept to the kan(r) gene is difficult because it may well be used as a marker in a large number of genetically engineered food crops.[99] It would appear from the general statutory and regulatory framework that the FDA should treat the kan(r) issue as one of a request for GRAS affirmation, to be determined on the basis of scientific consensus with respect to the data both available and submitted concerning the toxicity and general effect of kan(r)-engineered plants. The FDA has not yet published any official response to the Calgene advisory opinion request as of this writing.[100]

VIII. A Case Study of a New Animal Drug: r-BST

After years of controversy, the FDA recently approved the sale of

---

C.1.

97. *Id. See also* Redenbaugh et al. n.59.

98. FDA Statement, *supra* note 34, at 22,999 (Figure 4).

99. If kan(r) is used as a marker in ten or twelve common food plants, such as tomatoes, corn, wheat, and some fruits, would it be a "macroconstituent?" Would each subsequent manufacturer have to calculate the probable aggregate consumption in an "average" adult diet taking into account the additional impact of its product, or should the first manufacturers be required to project ahead to the probable aggregate consumption based on the other products which are likely to be introduced? Neither approach would lead to any firm consumption numbers nor would the criteria for making a decision be at all clear.

100. On April 8, 1994, an FDA Advisory Committee, the Food Advisory Committee, completed a hearing on the Calgene tomato. No safety concerns were raised and FDA Commissioner David Kessler was quoted as stating that final FDA action approving Calgene's petition would come within 90 days. Philip Hilts, Genetically Altered Tomato Moves Towards U.S. Approval, N.Y. Times, April 9, 1994, p. 7, Col. 4.

recombinant bovine somatatropin (r-BST) as a new animal drug.[101] Food additives exclude new animal drugs, biologics, and pesticides, because the food safety considerations for those substances are separately regulated under other statutes. As argued above, if an additional growth hormone gene were engineered into calf embryos, or even if a strong promoter gene were engineered into the embryo to increase the expression of bovine somatatropin substantially, it is quite possible that the increased level of r-BST in the offspring of the resulting animals would be regulated as a food additive or as a GRAS substance. This would be true regardless of whether the gene or gene promoter was of inter-generic or intra-generic origin. With current technology, however, it is easier to produce the desired enzyme in a culture or fermentation process and inject it into the animal, rather than to engineer it into embryos. Thus, r-BST and other such products of recombinant DNA technology intended for use in food animals will be regulated as either a new animal drug by the FDA[102] or as an animal biological by the USDA under the Virus-Serum-Toxin Act.[103]

While the dividing line between animal drugs and animal biologicals is not a sharp one,[104] in the "test case" of r-BST the FDA might also be viewed as a more credible regulatory body by consumers than the traditionally "pro-farmer" USDA. In any event, the FDA was the lead agency with jurisdiction over r-BST. The FDA's approval of a new animal drug requires that the applicant for approval of a new drug provide a method of assaying its presence in the food derived from the animal[105] as well as the proposed tolerance or residual level that shall be permitted to remain in or on the food without it being considered adulterated under the FDCA.[106]

In general, an application for the marketing of a new animal drug or biologic should be supported by data which address the safety, efficacy and tolerance issues, since the burden of proof as to safety and efficacy is on the manufacturer. Thus, tests would ordinarily include measurement of the concentrations of the proposed product or its me-

---

101. *See* Hotz, *supra* note 9.

102. 21 U.S.C. §§ 351, 352, 355 (1988 & Supp. IV 1992).

103. 21 U.S.C. §§ 151-159 (1988).

104. Animal biologicals achieve their intended effect primarily through interaction with the animal immune system, for example, vaccines. *See* Eugene I. Lambert, *Food and Drugs for Animals Other Than Man: More Equal Than Others*, *in* FOOD AND DRUG LAW 318, 319 (Richard M. Cooper ed., 1991). *See also* Jones, *supra* note 79.

105. 21 U.S.C. § 360b(b)(1)(G).

106. 21 U.S.C. § 360b(b)(1)(H).

tabolites in any edible tissues or food products from animals treated with the proposed product (the residue); toxicological studies on rodents or other species to determine what levels, if any, of the proposed product are toxic when ingested; and, based on the residual levels found and the level of toxicity, a suggested tolerance level. In some cases, where the residual level appears to be close to the toxic level, data showing that the residual level reaches apparent safety after a recommended withdrawal period can be submitted, along with a proposal for a tolerance level based on the recommended withdrawal period.[107] In the case of a product that produces any toxic residue or metabolite, in addition to determining a safe tolerance level that protects human health, it is necessary to provide the FDA with a means for measuring concentrations in food products derived from treated animals, to assure that food products are unadulterated by over-dosage, failure to follow the withdrawal schedule, or by any other mechanism.[108]

The application to market r-BST for increased milk production was questioned as to every statutory requirement with the exception of efficacy for the proposed labeled use (increasing milk production). Critics have debated its safety for the cows in light of some reports of increased mastitis in treated herds; safety for humans consuming milk from r-BST-treated cows; and, the necessity for setting tolerance levels for r-BST in milk or beef, or for other hormones stimulated to higher levels in the milk or meat of r-BST-treated cows.[109] The FDA's long-awaited approval of r-BST has provoked considerable criticism from segments of the dairy industry, from some scientists, and from the general public.[110]

While a complete review of the data relied upon by the FDA in its

---

107. The withdrawal period is based on experiments designed to show what levels of the substance are found in edible portions of the animal upon slaughter at varying internals after the last administration of the experimental substance. The experimental data generated is then used to establish the minimum period between last administration and slaughter (the withdrawal period) which allows the substance to be metabolized to safe (or in some cases undetectable) residual levels.

108. 21 U.S.C. § 360b(b) (1992).

109. Samual S. Epstein, *Potential Public Health Hazards of Biosynthetic Milk Hormones*, 20 INT'L J. HEALTH SERV. 73, 78-79 (1990). *See also* Dept. of Health and Human Services Public Health Service Memorandum from the Director, State Training and Information Branch to State Health Officers and Others on the Subject of Bovine Somatotropin, (Oct. 6, 1989) [hereinafter HHS/PHS Memo].

110. *See* Hotz, *supra* note 9; Sally Lehrman, *Drug to Boost Cow's Output Not an Easy Sell*, THE SAN DIEGO UNION-TRIB., Nov. 12, 1993 at C2. *See also* D.S. Kronfeld, *Letter to the Editor*, 265 JAMA 1389 (1991) (responding to the FDA's earlier decision to allow marketing of milk from test herds of r-bst-treated cattle).

determination that r-BST milk is safe for human consumption is beyond the scope of this chapter, it is fair to say that the overwhelming scientific consensus supports the FDA's determination.[111] In fact, the FDA's treatment of r-BST closely parallels the analysis for newly introduced proteins in its Statement of Policy for New Plant Varieties. The close relationship between the two analyses is chiefly attributable to the fact that r-BST is a protein hormone.[112] To paraphrase the eminent food safety expert Gertrude Stein, a protein is a protein is a protein, and thus r-BST in milk is conceptually (if not legally) the same as a recombinant additional corn protein in corn. It is digested like all other proteins. In addition, it is not an allergen or one of the very rare (e.g. snake venom-derived) toxic proteins. Furthermore, even when injected in humans the natural bovine hormone has been found to be biologically inactive.[113] Finally, because cows' milk naturally contains levels of endogenous bst, the administration of r-bst results in no new substances being found in the milk.[114]

IX. Conclusion: Risk Perception and Food Biotechnology

If the Calgene tomato and r-BST are so unlikely to pose any risk, what then is behind the furor over food biotechnology, besides twenti-

---

111. *See, e.g., NIH Technology Assessment Conference, Statement on Bovine Somatotropin*, 265 JAMA 1423-25 (1991) [hereinafter NIH Statement]. With respect to the tolerance issues, the FDA based its position that no tolerance was required because any substances that were in the milk of treated cows would be indistinguishable in kind from those found in the milk of untreated cows and would not differ significantly in quantity.

112. Hormones are of a variety of types, but two basic groups are protein hormones and steroidal hormones. Steroidal hormones are all synthesized from cholesterol, either artificially, or by the body itself, but all have the basic structure of cholesterol with various active groups placed on it. The anabolic steroids, the estrogen hormones (including diethyl stilbesterol, or DES) and the adrenocortical hormones are all steroid hormones. Insulin, growth hormone, and erythropoetin are all protein hormones. For food safety purposes, the key difference between the two types of proteins is that steroid hormones can be orally administered (e.g. oral contraceptives, or birth control pills) because, being cholesterol-based, they are not digested by proteases in the digestive tract. On the other hand, protein hormones cannot be orally administered, as they are quickly digested by proteases. Thus insulin-dependent diabetics have long had to learn to self-inject their required hormone. *See* HHS/PHS Memo, *supra* note 102; Van Nostrand's Scientific Encyclopedia, entries for hormones, insulin, steroid.

113. *See* NIH Statement, *supra* note 111. Bovine growth hormone is species limited, meaning that although it may be active in species other than cows, it is not active in humans and other primates.

114. Although no new substances are found in the milk of cows treated with r-bst, critics have focused on the higher average levels of bst and insulin-like growth factor (IGF-1) in the milk of treated cows. Epstein, *supra* note 102, at 79. The average levels of these protein hormones, however, do not exceed the upper-range of levels found in untreated cows. *See* NIH Statement, *supra* note 111.

eth century luddism? Understanding the controversy fully requires not merely an understanding of the scientific and regulatory issues, but also an understanding of the dynamics of public risk perception and the influence of that perception on the legal and regulatory processes. The prolonged and costly struggle over r-BST makes it clear that the prudent biotechnology company will attempt to take probable public response into account.[115]

For better or for worse, our system is one in which both the Congress and the executive branch agencies, which design and implement the regulatory framework for biotechnology, are sensitive to public concerns.[116] While it is all very well for a biotechnology company, rooted in a deep faith in science in general and its own science in particular, to take comfort in the sort of objective risk assessment framework exemplified by the FDA Statement of Policy for New Plant Varieties, public risk perception is highly qualitative, rather than objectively quantitative.[117] For an extreme example, it is far safer to eat Alar-treated apples than to ski downhill at Vail, but many of those downhill skiers are likely to be concerned about trace pesticide residues in their food.

There is an excellent body of literature that explores the factors influencing this "subjective" risk perception.[118] To summarize the literature on risk perception, it is fairly clear that high up on the list of the factors that magnify the public perception of a risk are its voluntariness, controllability, complexity, and the newness of the technology producing the risk. Examining the applications of these factors to food safety in general, it is clear that the "hidden" risks of food biotechnology food additives or ingredients would cause grave public concern because of all of those important variables. The risk is involuntary (at least to the extent that there is no special labeling of such foods), un-

---

115. "From the broader perspective of genetically engineered food products, the milk hormone is one of the worst products the industry could have started with. . . . Milk is something people consider natural and sacred. They don't want to see it manipulated." Nachama Wilker, Executive Director of the Boston-based Committee for Responsible Genetics, quoted in Hotz, *supra* note 9.

116. Robert A. Bohrer, *The Future Regulation of Biotechnology*, in FROM RESEARCH TO REVOLUTION: SCIENTIFIC, BUSINESS AND LEGAL PERSPECTIVES ON THE NEW BIOTECHNOLOGY 101, 110-12 (1987).

117. Thus the possible boycott of genetically engineered foods by prominent chefs, Hotz, *supra* note 9.

118. *See, e.g.*, Paul Slovic et al., *Facts and Fears: Understanding Perceived Risk* in SOCIETAL RISK ASSESSMENT (Richard C. Sclwing & Walter A. Albers, Jr. eds., 1980); Committee on Risk and Decisionmaking, National Academy of Sciences, Risk and Decisionmaking: Perspectives and Research (1982).

controllable, complex, and stems from an extremely new technology. This does not mean that no application of biotechnology to food will find public acceptance. Rather, it means that public acceptance may hinge on the perceived benefit of the new technology to offset the perceived risk. Thus, biotechnology applications that fill a strongly perceived public need are likely to win acceptance more easily than those which merely increase producer or farmer profits. At least in part for that reason, early applications for the testing and marketing of biotechnology-produced biopesticides that replace chemical pesticides have received minimal public attention and relatively speedy regulatory approval.[119] The lesson for the biotechnology industry is clear. Product development that takes into account the subjective nature of public risk perception is likely to pay off both in increased sales and in much faster regulatory approval. The long delays and stormy history of r-BST are an example of the cost of ignoring such concerns. Calgene may also learn that, despite government approval, the time is not yet ripe for the FLAVR SAVR(TM) tomato.

---

119. E.g. the recombinant bacillus thuringensis endotoxin marketed by Mycogen Corp., Greg Johnson, *Mycogen Cats OK to Market Bio-insecticide*, L.A. TIMES (San Diego County Ed.), June 28, 1991, at B1; Lawrence M. Fisher, *Business Technology*, THE NEW YORK TIMES, July 17, 1991, at D1.