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An Agricultural Law Research Article

The Biotechnology Revolution and Its Regulatory Evolution

Part 1

by

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Originally published in DRAKE LAW REVIEW
38 DRAKE L. REV. 471 (1989)

DRAKE
LAW REVIEW

Volume 38 1988-1989 Number 3

THE BIOTECHNOLOGY REVOLUTION AND ITS REGULATORY EVOLUTION

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Is biotechnology a unique technology that will revolutionize life as we know it or simply an expedited version of natural processes that have been with us since the beginning of life? The answer may depend on what "camp" you are in or for what purpose you are defining the term.[1] Those

1. Biotechnology is not a precisely defined term, nor is it a single technology. At its most comprehensive, the term has been defined as the "application of biological systems and organisms to technical and industrial processes." Young & Miller, *Comment: Biotechnology: A 'Scientific' Term in Name Only*, 6 BIOTECH. L. REP. 11 (1987). This broad definition includes such traditional biological methods as plant and animal breeding and fermentation. A more modern and narrow definition of the term would encompass the ability to effect specific genetic changes via such techniques as those which involve recombinant DNA (R-DNA) (*i.e.*, joining together pieces of DNA from different organisms together in vitro) and cell fusion (used to create monoclonal antibodies—homogeneous antibodies that recognize only one kind of antigen). This definition was adopted by the Office of Technology Assessment (OTA) in its publication: OFFICE OF TECHNOLOGY ASSESSMENT, COMMERCIAL BIOTECHNOLOGY: AN INTERNATIONAL ANALYSIS, 3-4, 503 (1984). More recently recombinant RNA (RRNA) has been added to the techniques of biotechnology. This technique is the modification of RNA by insertion of segments of foreign

who would like to see biotechnology processes and products more stringently regulated have argued that biotechnology is a new technology with dangers and risks never before confronted by our society.[2] Those who want to see fewer restrictions on biotechnology research and development have argued that it is really nothing new, that it poses no new risks or risks that are different in kind from existing biological and chemical processes.[3] The essence of this debate, which is continually renewed in the scientific and regulatory literature, is well captured in this statement by Congressman Florio:

> The Cassandras talk clearly of Andromeda strains, of developments that would change the ecology of the earth in a relatively short period of time. The Babbitts scoff at that gloom, dismissing past mistakes as minor laboratory accidents, explaining about the implications of thwarting innovation and suffocating this fledgling industry in an irrational overreaction to extremely remote events.[4]

These divergent views about the risks and regulation of biotechnology have characterized the technology since its inception. As the science has progressed, however, the perceptions of the risks associated with the technology have changed and the regulatory system has been modified to keep pace with them—waxing when the risks are perceived as great and slowly

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RNA. For purposes of this paper, "biotechnology" will be used in its more narrow sense and will be used interchangeably with the term "genetic engineering."

2. *See, e.g.*, Wald, *The Case Against Genetic Engineering*, 16 THE SCIENCES 7-8, 10-11 (Sept.-Oct. 1976), in which Wald states that "[R]ecombinant DNA technology fills our society with problems unprecedented not only in the history of science, but of life on the Earth." *Id.* at 7. *See also* Ruckelshaus, *Risk, Science, and Democracy*, 1 ISSUES IN SCI. TECH. 19, 21 (Spring 1985) (the author claims that the risks inherent in biotechnology are the largest our society has ever faced from advances in the natural sciences).

3. *See, e.g.*, Levin & Harwell, *Environmental Risks and Genetically Engineered Organisms*, in BIOTECHNOLOGY IMPLICATIONS FOR PUBLIC POLICY 66 (S. Panem ed. 1985) [hereinafter Panem] ("Many have assumed that such [genetically altered] organisms . . . represent something fundamentally new and different . . . . This assumption is incorrect . . . . Genetic engineering techniques can be viewed simply as a more efficient means of modification than have been accomplished by the more expensive, time-consuming, and less efficient conventional processes of mutation, selection and breeding programs."). *See also* THE RECOMBINANT DNA DEBATE 18 (D. Jackson & S. Stich eds. 1979) ("There is substantial uncertainty as to whether the risks associated with the careful application of recombinant DNA methods to a study of living organisms are any greater than those posed by conventional genetic and microbiological research for over 50 years."); NATIONAL ACADEMY OF SCIENCES, INTRODUCTION OF RECOMBINANT DNA-ENGINEERED ORGANISMS INTO THE ENVIRONMENT: KEY ISSUES 8, 22 (1987) [hereinafter NAS REPORT] ("There is no evidence that unique hazards exist either in the use of RDNA techniques or in the transfer of genes between unrelated organisms."); LAW OF ENVIRONMENTAL PROTECTION § 18.02(4)(d) (S. Novick, D. Stever, & M. Mellon eds. 1987) [hereinafter Novick] ("To date, ecologists have not identified any new adverse ecological consequences which flow directly from the method by which organisms were engineered . . . . Some ecologists even refuse to distinguish among traditional and advanced methods of genetic engineering in discussing environmental risk.").

4. Florio, *Regulation in Biotechnology*, in Panem, *supra* note 3, at 42.

waning as new information is gained and perceptions of the risks decline.

This article traces the evolution of the regulation of biotechnology, tying it to our knowledge and perceptions of its risks and benefits. The article also speculates about future regulatory issues that will arise as biotechnology continues to expand and move into new areas. Part I of the article briefly summarizes the current status of biotechnology and its potential benefits. Part II looks at the perceived risks associated with biotechnology both past and present. Parts III through VIII describe the existing regulatory structure for biotechnology and its historical development. Although this section focuses on federal regulations, it also includes a discussion of state and local regulations and court cases regarding the regulation of biotechnology. Part IX assesses the adequacy of the regulatory structure. Part X identifies new areas which the regulatory system may have to address in the coming years and ways in which the regulatory system might be improved and a greater consensus regarding regulatory policies achieved.

I. Biotechnology—Current and Potential Benefits

The use of biotechnology techniques is already providing a wide range of benefits to society.[5] Current applications have as their primary focus five areas: (1) development of human therapeutics; (2) animal health care and development; (3) plant agriculture; (4) food production; and (5) environmental management.

In the area of human therapeutics, researchers and developers are using biotechnology to produce naturally occurring human drugs more efficiently and in greater quantities than the body itself can generate, and to produce new drugs and vaccines to fight such diseases as AIDS, cancer, hepatitis B, herpes, rabies, and influenza.[6] Biotechnology is also being used to prevent

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5. According to a recent General Accounting Office report:

> Compared with conventional processes (plant breeding or selection of randomly produced mutant microbes), [R-DNA] techniques offer a more precise means of creating many products. They can also dramatically shorten the time required to perform certain biological processes, such as producing new strains of plants and animals. Most strikingly, the new genetic engineering has made it possible to transfer genes between very different kinds of organisms—something not previously achievable.

General Accounting Office, Biotechnology: Managing the Risks of Field Testing Genetically Engineered Organisms 9 (1988) [hereinafter GAO Report].

6. Some of the "commercialized fruits" of recombinant DNA and monoclonal antibody technology include human insulin developed using R-DNA techniques, human growth hormone, hepatitis B vaccine, interferon alpha (a protein which has shown promising results against cancer and viral diseases), veterinary vaccines, diagnostic test kits for numerous conditions, and tissue plasminogen activator (a blood clot dissolving protein used to treat heart attack victims). Currently in the clinical trial phase are such promising products as erythropoietin (EPO), a peptide that alleviates anemia in kidney dialysis patients; tumor necrosis factor (TNF), natural body factors that attack cancer; and factor VIII, an agent to promote blood clotting in hemophiliacs. Under study are vaccines for AIDS, herpes, and rabies; prourokinase, a clot-dissolving substance that may have value in treating heart disease; superoxide dismutase (SOD), a

diseases. For example, scientists at the National Institutes of Health (NIH) and some universities are genetically altering mosquitoes to prevent the spread of malaria and yellow fever. Finally, R-DNA may soon be used to treat genetic diseases by deliberately introducing fragments of "therapeutic" genes into the cells of human patients.[7]

Animal health care and breeding are also "fertile" grounds for biotechnology. In the area of animal drugs, some of the products already approved or on the market include monoclonal antibodies to prevent calf diarrhea and to treat a serious swine disease called pseudorabies. In the area of animal growth and development, products being clinically tested include porcine growth hormone, which stimulates growth in young pigs, and an R-DNA-derived bovine growth hormone to speed up the growth of cattle. Under study are animal cloning techniques to produce animals with certain properties—such as increased milk production and disease resistance.[8]

Of the numerous uses of biotechnology, agricultural applications are considered among the most promising. Scientists are developing crops that are more nutritious, bigger, and more resistant to insects, herbicides, frost, and disease. Agricultural companies are also focusing their attention on the development of genetically engineered microbial pesticides which would reduce our dependence on chemical pesticides.

Biotechnology is also making its mark in the food production industry. The development of new and improved enzymes and the use of fermentation processes has put food production in the forefront of biotechnology applications. These new processes are enabling food manufacturers to raise yields and reduce waste and energy costs.[9]

Finally, in the area of environmental management, biotechnology is be-

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substance that may prevent tissue damage from heart attacks; neurotrophic growth factors, which may stimulate nerve growth in patients suffering from degenerative brain disorders; and epidermal growth factors, which speed wound healing. *See Biotechnology Growing Greener at Last*, CHEMICAL WEEK 20 (Sept. 30, 1987), for a more detailed description of recent applications of biotechnology in the pharmaceutical area.

7. A preliminary proposal to begin human trials of such "human gene therapy" was submitted to the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health in the spring of 1987 for review. Telephone interview with William Gartland, Director, NIH Office of Recombinant DNA Activities, in Bethesda, Md. (July 5, 1988). Additional safety studies have been requested by the reviewers before the initiation of clinical trials. *Id. See also* N.Y. Times, Oct. 20, 1988, at B9, col. 1.

8. The Agricultural Research Service within USDA is working on two research projects involving genetically engineered animals. One entails studies of sheep and swine that have been altered by the addition of an extra gene for growth hormone. The objective of this work is to improve production characteristics such as the animal's growth rate and the fat content of its meat. The second project entails engineering chickens to be resistant to the avian leukosis virus, which causes a serious poultry disease. *See* OFFICE OF TECHNOLOGY ASSESSMENT, FEDERAL REGULATION AND ANIMAL PATENTS (1988). *See also* Schneider, *Better Farm Animals Duplicated by Cloning*, N.Y. Times, Feb. 17, 1988, at A1, col. 3.

9. *See World Food Congress: Biotech Yields Better Enzymes, Crops, and Pigs*, 6 BIOTECH. 14 (1988).

ing used for the recovery of precious metals from refractory ore bodies, pollution control, toxic waste degradation, and ethane and oil recovery. Naturally-occurring microorganisms capable of degrading toxins like aldrin, DDT, and kepone have been isolated and show promise as a means of cleaning up hazardous waste.[10]

II. The Risks of Biotechnology

Since 1972, when the first biotechnology experiments were conducted, the risks associated with at least some types of biotechnology—specifically R-DNA—have been hotly debated. The debate, at least initially, was fueled by scientists themselves: unsure of the risks associated with this new technique, they engaged in a two-year self-imposed moratorium on R-DNA experimentation.

Initial concerns regarding R-DNA experiments focused on two areas: (1) harmful effects on human health and the environment ("health and safety risks") and (2) deleterious effects on society ("social risks"). Environmental and human health risks were believed to arise from the possibility that "harmful man-made organisms, organisms with new treatment-resistant properties, or new biological life forms with superior survival characteristics enabling them to displace existing beneficial organisms,"[11] would escape from the laboratory. Social risks were said to arise from our new ability to play God by developing new species at an increasingly rapid rate and potentially by altering human beings by changing their genetic structure.[12]

After the moratorium ended and scientists began to conduct R-DNA research and to develop experience with the technique, most researchers be-

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10. *See* Novick, *supra* note 3, at § 18.01(3).

11. Naumann, *Federal Regulation of Recombinant DNA Technology: Time for Change*, 1 High Tech. L.J. 61, 61 (1986) [hereinafter Naumann].

12. Engelhard has distinguished social risks from physical risks on the basis that social risks "flow from the disruptive effects of new theories and data on existing values and beliefs." *See* Capron, *Prologue: Why Recombinant DNA?*, 51 S. Cal. L. Rev. 973, 977 (1978). In an article in MIT's *Technology Review*, Robert Sinsheimer summarized the bases for concerns regarding social risks:

> For 3 billion years, natural changes in the number, structure, and organization of genes have determined the course of evolution. We have now come to the end of that familiar pathway . . . . We now possess the ability to manipulate genes, and we can direct the future course of evolution . . . . We can plan, and with computer simulation ultimately anticipate the future forms and paths of life. Mutation and natural selection will continue, of course. But henceforth, the old ways of evolution will be dwarfed by the role of purposeful human intelligence. In the hands of the genetic engineer, life forms could become extraordinary Tinkertoys and life itself just another design problem.

Regal, *The Ecology of Evolution: Implications of the Individualistic Paradigm*, in Engineered Organisms in the Environment: Scientific Issues 12 (O. Halvorson, D. Pramer & M. Rogul eds. 1985) (quoting Sinsheimer, *Genetic Engineering: Life as a Plaything*, Tech. Rev. April 1983, at 14).

lieved that the initial environmental and human health risks had been greatly exaggerated and there developed a consensus, at least in the scientific community, that R-DNA research conducted in the laboratory was a relatively safe activity.[13]

As science has progressed and R-DNA techniques have come out of the laboratory and into the field for testing, attention has turned to the risks associated with the deliberate release of genetically altered organisms into the environment.[14] Although most scientists believe that the risks of such deliberate release experiments are overrated, many will admit that there is a very small probability of serious harm.[15]

A. *Environmental and Human Health Risks*

Concerns regarding deliberate release experiments center on the fact that the organisms used are designed to survive in the environment long enough to perform a designated task. This is in contrast to laboratory microbes which typically die outside the laboratory. Not only may such microbes survive, but also, unlike ordinary inert pollutants, they may multiply and spread, making them difficult to control.[16]

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13. *See* Green, *Genetic Technology May Prompt New Legal Regime*, Legal Times of Washington, Jan. 18, 1982, at 17 ("The original perception of recombinant DNA activities as involving special hazards has been swept away by a revisionist sentiment that has prevailed since 1978.") [hereinafter Green].

14. The first genetically engineered organism was approved for release by NIH in 1981. By 1985 there was a backlog of proposals to release genetically engineered organisms into the environment at the federal agencies charged with approving such releases. Also in that year a GAO study revealed that the USDA was funding at least eighty-seven projects involving the environmental release of genetically engineered organisms and that the majority of these releases would occur in the next five years. SUBCOMM. ON INVESTIGATIONS AND OVERSIGHT, HOUSE COMM. ON SCIENCE AND TECHNOLOGY, 99TH CONG., 2D SESS., REPORT ON ISSUES IN THE FEDERAL REGULATION OF BIOTECHNOLOGY: FROM RESEARCH TO RELEASE (Comm. Print 1986) [hereinafter SUBCOMMITTEE REPORT]. In May 1986 the first authorized release of a genetically-engineered organism occurred in Middleton, Wisconsin, when Agracetus Corporation planted two hundred tobacco plant seedlings that had been genetically-altered to be resistant to a specific disease. *See id.* Since then, at least twenty other deliberate release experiments have been conducted in the United States. Approximately five of these involved microorganisms, including the ice-minus (*Pseudomonas syringe)* bacteria released by AGS, Inc., and Steven Lindow in California; the *Pseudomonas fluorescens* marker, released by Monsanto in Modesto, N.C., the genetically engineered *Rhizobium meliloti* released by Biotechnica International to increase nitrogen fixation in alfalfa in Pepin County, Wisconsin; and Crop Genetics International's release in Beltsville, Maryland, of bacteria to make corn resistant to corn borers. The remaining releases have primarily involved genetically engineered plants. Telephone interview with Steven Witt, President, Center for Scientific Information, in San Francisco, California (July 5, 1988).

15. Some have termed this a "low probability/high consequence" risk and have likened it to the risk associated with nuclear power plants. *See, e.g.*, Note, *The Rutabaga That Ate Pittsburgh*, 72 VA. L. REV. 1529, 1560 (1986) [hereinafter Note, *Rutabaga*]. *See also* Gore & Owens, *The Challenge of Biotechnology*, 3 YALE L. & POL. REV. 336, 342 (1985).

16. *See* Note, *Rutabaga, supra* note 15, at 1534. *See also* Sharples, *Regulation of Products from Biotechnology*, 13 POL'Y F. 1329 (1987).

These factors have raised concerns about the potential impact of deliberate releases of genetically engineered organisms on the public health and the ecosystem. In order to affect human health, any organism must:

1. be able to survive and multiply in the environment;
2. be of a type that could infect humans;
3. be able to resist a wide range of host defense mechanisms; and
4. produce a factor that can cause disease (*i.e.*, a pathogen).[17]

The concern with genetic engineering, however, is not whether it will be used deliberately to produce organisms that cause disease but whether it will exacerbate or facilitate the disease producing potential of naturally occurring organisms. Since in most cases human pathogens are not going to be "released knowingly" into the environment,[18] concern has focused on the possibility that R-DNA technology might accidentally convert a nonpathogen to a pathogen. Such an accident is considered unlikely by most scientists. A recent report—*Introduction of Recombinant DNA-Engineered Organisms into the Environment* published by the National Academy of Sciences (NAS)—concludes that "the possibility that minor genetic modifications with R-DNA techniques will inadvertently convert a nonpathogen to a pathogen is . . . quite remote."[19]

As a result, concerns about harms caused by pathogenic organisms to humans and animals have moved to the back burner while concerns about damage to the environment and the ecosystem caused by genetically engineered nonpathogens have moved to the forefront in the deliberate release debate. The concern in this area, however, does not appear to stem from the fact that the organisms are genetically engineered. In fact, scientists generally agree that "[t]he risks of [releases] arise from the way the organisms may interact with their environments, rather than from their having been genetically engineered."[20] Thus, as was the case with their disease producing capability, the key issue is whether the genetically engineered organisms have acquired traits that give them "an undesirable competitive advantage over unaltered organisms."[21]

Ecologists often cite examples of the introduction of exotic species into new environments, such as the "introduction to the United States of the Brazilian water hyacinth in the late 19th century which led to an infestation

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17. *See* OFFICE OF TECHNOLOGY ASSESSMENT, IMPACTS OF APPLIED GENETICS: MICRO-ORGANISMS, PLANTS, AND ANIMALS 201 (1984) [hereinafter OTA, IMPACTS OF APPLIED GENETICS]. *See also* J. AREEN, P. KING, S. GOLDBERG & A. CAPRON, LAW, SCIENCE & MEDICINE 114-17 (1984) (quoting NATIONAL INSTITUTES OF HEALTH, FINAL ENVIRONMENTAL IMPACT STATEMENT ON NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES 23-37 (Oct. 1977)).

18. *See* Novick, *supra* note 3, at § 18.02[2].

19. NAS REPORT, *supra* note 3, at 15.

20. GAO REPORT, *supra* note 5, at 16. *See, e.g., Genetic Changes in Plants May Lead to Fortified Weeds*, Wash. Post, Oct. 3, 1988, at A3, col. 1, which states that the greatest danger posed by genetic engineering of plants may come from their breeding with weeds.

21. GAO REPORT, *supra* note 5, at 16.

of the Southern waterways" or the "uncontrolled spread of English sparrows originally imported to control insects," as a basis for concern regarding the deliberate release of genetically engineered organisms.[22]

The appropriateness of such analogies, however, is a subject of considerable disagreement. Some argue that genetically engineered organisms, which typically carry less than one percent new genes, are over ninety-nine percent the same as the original, and thus are "not analogous to the 'totally new' organisms introduced into an ecosystem."[23] The NAS report states that situations in which exotic species are introduced into new environments are not analogous to those in which R-DNA-engineered organisms are "reintroduced" into the environment from which the original non-modified organisms were taken. Such analogies may be appropriate, however, for introductions involving R-DNA-engineered organisms taken from quite different environments or geographic locations.[24]

In the deliberate release experiments conducted to date, there have been no measurable harmful effects to the environment or to humans.[25] Thus, we are left with the best estimates of researchers and scientists as to what we can expect in the way of risks, and, unfortunately, there is widespread variation in estimation. In a 1986 report, Fiksel and Covello remarked:

> Scientists have expressed a number of disparate views about the potential risks of releasing genetically modified microorganisms. For example, one ecologist has suggested that the outcome of introducing a new species is not predictable, since there is at present no systematic understanding of the natural factors that influence its success or failure in the environment. Another ecologist has suggested that the probabilities of survival and establishment are small, but that the potential consequences may be significant. A contrary view, expressed . . . by an Assis-

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22. OTA, IMPACTS OF APPLIED GENETICS, *supra* note 17, at 200. Other examples of harm caused by the introduction of non-native microorganisms into new environments include the bubonic plague, the periodic appearance of foot-and-mouth disease in the United States, and the disappearance of our native American chestnuts due to chestnut blight. Similar disruptions have also resulted from the introduction of foreign insects such as gypsy moths and Japanese beetles and foreign animals such as starlings and mongoose. *See* Sharples, *Spread of Organisms with Novel Genotypes: Thoughts from an Ecological Perspective*, RECOMBINANT DNA TECH. BULL. 43, 49 (June 1983).

23. OTA, IMPACTS OF APPLIED GENETICS, *supra* note 17, at 200.

24. NAS REPORT, *supra* note 3, at 19. *See also* Panem, *supra* note 3, at 56-64 (discussing the appropriateness of such analogies).

25. *But see Argentines Report Infection by Altered Farm Virus*, N.Y. Times, Jan. 22, 1988, at A32, col. 1. According to Argentinian scientists, farmworkers in Argentina were accidentally infected by a genetically engineered anti-rabies virus when innoculating cattle with a vaccine against the virus. This claim is the subject of considerable dispute, however. Researchers from the Wistar Institute in Philadelphia, Pennsylvania, who helped develop the vaccine, had not been given data on which to evaluate the Argentinian claims and argued that such an accident did not make any scientific sense. *See* Fox, *Biotechnology Alfresco*, 38 BIOSCIENCE 533, 534 (1988) (full discussion of the debate).

> tant Secretary of the Department of Agriculture, suggests that "nature is resilient," and that ecological balance cannot easily be disrupted by the introduction of a genetically modified microorganism. [26]

Two more recent reports—one by the NAS and the other by the U.S. Congress' Office of Technology Assessment (OTA)—also provide evidence of the divergent views regarding the risks of biotechnology. The NAS report concluded:

> There is no evidence that unique hazards exist either in the use of R-DNA techniques or in the transfer of genes between unrelated organisms . . . . [The] risks associated with the introduction of R-DNA engineered organisms are the same in kind as those associated with the introduction into the environment of unmodified organisms modified by other genetic techniques.[27]

The OTA report, somewhat more cautiously, concluded:

> Planned introductions of genetically engineered organisms into the environment . . . are not . . . without potential risks. Virtually any organism deliberately introduced into a new environment has a small but real chance of surviving and multiplying. In some small subset of such cases, an undesirable consequence might follow. The complexity of even simple ecosystems makes the precise prediction of such events, and of their consequences, difficult.[28]

This diversity of views has made it especially difficult for regulators to develop an acceptable regulatory framework for addressing the health and environmental risks of deliberate release experiments.

Much of the disparity in views can be attributed to differences in perspective regarding the adequacy of data on which to base predictions of ecological risk. Those who are unwilling to discount the risks of the technology argue that assessing ecosystem effects of genetically engineered organisms is a highly speculative endeavor because virtually no data exist from which ecologists can extrapolate to make predictions.

Those who see the risks as minimal take a different view. The recent NAS report argues that "[t]here is a large body of relevant knowledge on the ecological consequences of biological introductions as well as on the genetic modification of organisms by traditional breeding methods."[29] The report also points to the fact that R-DNA techniques have been in use for more than fifteen years "in hundreds of laboratories around the world" and

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26. Fiksel & Covello, *The Suitability and Applicability of Risk Assessment Methods for Environmental Applications of Biotechnology*, BIOTECHNOLOGY RISK ASSESSMENT 2, 3 (1986).

27. NAS REPORT, *supra* note 3, at 6.

28. OFFICE OF TECHNOLOGY ASSESSMENT, NEW DEVELOPMENTS IN BIOTECHNOLOGY: FIELD TESTING ENGINEERED ORGANISMS: GENETIC AND ECOLOGICAL ISSUES 3 (1988) [hereinafter OTA, FIELD TESTING ENGINEERED ORGANISMS].

29. NAS REPORT, *supra* note 3, at 7.

that during that time, "thousands of different organisms have been modified and their characteristics studied."[30] Critics of the report argue, however, that such data are not wholly applicable to assessing the risks of deliberate releases; it is argued that laboratory data are irrelevant to the effects of the organism in the environment.

B. *Social Risks*

The social risks of a technology derive from its ability to change our social fabric, beliefs, and values. In the area of biotechnology such risks might include changes in the way we think about life, death, conception, birth, disease, health, the natural environment, and the relationship of humans to animals. The social risks of biotechnology have been virtually ignored by scientists conducting research in the area. Rather, it has been the public at large along with ethicists and philosophers who have brought the social risks to light. A 1986 Harris poll on public perceptions of biotechnology found that twenty-two percent of Americans believe that genetic engineering will make life worse for them and others rather than better. Whether this feeling is based on concerns about social risks is unclear; however, the survey results point out that the public has nagging concerns about biotechnology that have not been addressed.[31]

Most of the discussion regarding the social risks of biotechnology has focused on the human applications of biotechnology processes rather than on the environmental applications. This appears to parallel public concerns. The 1986 Harris poll found that forty-two percent of the public believe that human cell manipulation via genetic engineering is morally wrong, while only twenty-six percent believe that genetic alteration of plants, animals, and bacteria is morally wrong.[32] Members of the public have expressed anxiety about some biotechnological procedures in large part because of their relationship to controversial reproductive issues, *i.e.*, abortion of defective fetuses, sex selection, and human gene therapy.[33]

Two types of human gene therapy—human germline and enhancement

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30. *Id.* at 9. Similarly, the OTA report on field testing engineered organisms states that a sufficiently large body of data exists, chiefly concerning microbes introduced for biocontrol and agricultural applications, to allow scientists to accurately predict the outcomes of small-scale planned releases. *See* OTA, FIELD TESTING ENGINEERED ORGANISMS, *supra* note 28, at 16, 38-39.

31. The poll, conducted at the request of the Office of Technology Assessment, found that there was actually an increase in the percentage of those who felt that genetic engineering would make things worse for them. In a similar poll conducted in 1982, only sixteen percent of the public felt that biotechnology would decrease the quality of their lives and the lives of others. *See* OFFICE OF TECHNOLOGY ASSESSMENT, NEW DEVELOPMENTS IN BIOTECHNOLOGY—BACKGROUND PAPER: PUBLIC PERCEPTIONS OF BIOTECHNOLOGY 50 (1987) [hereinafter OTA, REPORT ON PUBLIC PERCEPTIONS].

32. *Id.* at 4.

33. *See* Green, *supra* note 13, at 17.

therapy—have probably provoked the greatest public concern.[34] Germline therapy involves the alteration of an individual's germ cells (reproductive cells) so that genetic alterations are passed on to one's offspring. Enhancement therapy is the modification of cells to produce different character traits—*i.e.*, height, hair color, eye color, intelligence—rather than medically therapeutic changes. Although the application of this type of therapy is decades away, the possibility of its application has moved several authors to raise the spectre of Huxley's *Brave New World* and to predict predetermination of the physical traits of future generations.[35] Others have raised a concern that genetic engineering could become a tool of social or economic control.[36]

More recently, significant public attention has focused on the federal government's undertaking to map and sequence the human genome. In the spring of 1988, seventy prominent national leaders announced their support for the creation of a congressional board and citizens' committee to address certain ethical issues that will arise from the Human Genome Project.[37] The leaders expressed concern that the mapping of the human genome could dramatically affect the private and public life of the country and that information gained from the project could lead to genetic discrimination and eugenics or could interfere with an individual's right of privacy.[38]

Another set of concerns in this area has religious overtones. Some argue that there should be no research in this area because the ability of scientists to transfer DNA from one species to another or to alter one's genetic structure smacks of "playing God."[39] Those in this camp further argue that there is something morally wrong with crossing species barriers—that there is

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34. Gene therapy is defined as "the introduction of a normal functioning gene into a cell in which its defective counterpart is active," and, in some cases, the excision of the defective gene. PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BEHAVIORAL RESEARCH, SPLICING LIFE: THE SOCIAL AND ETHICAL ISSUES OF GENETIC ENGINEERING IN HUMAN BEINGS 42 (1982).

35. Public concern was expressed in a 1982 New York Times editorial entitled "Whether to Make Perfect Humans." N.Y. Times, July 22, 1982, at A22, col. 1. The editorial suggested that the potential dangers of germline therapy were so serious that a ban on such therapy should be considered. "The remaking of man," said the Times, "deserves a little discussion." *Id.*

36. *See* Gore & Owens, *supra* note 15, at 353. In fact, this has become an issue with regard to the use of bovine growth hormone, which is currently being used to increase milk production in cows. Small farmers feel that the widespread use of the hormone will give large farmers a significant economic advantage and push the small farmer out of business.

37. In February 1988 the National Research Council Committee on Mapping and Sequencing the Human Genome found the Human Genome Project feasible and strongly urged that a $200 million a year effort to discover the location of every gene within human chromosomes begin immediately, stating that "such a special effort in the next two decades will greatly enhance progress in human biology and medicine." *See Genome Projects Ready to Go*, 7 BIOTECH. L. REP. 207, 208 (1988).

38. *Human Genome Policy Board Recommended*, 7 BIOTECH. L. REP. 105, 115 (1988).

39. *See* T. HOWARD & J. RIFKIN, WHO SHOULD PLAY GOD? (1977).

something sacred about the genetic composition of a species.[40] These concerns appear to suggest that "recombinant DNA could someday surface means of destruction that ought not to be published."[41] As yet, there has been no satisfactory resolution of these issues and the legal community, like the scientific community, has focused little attention on them.

III. Regulatory Evolution

The regulation of biotechnology has been evolving since 1976 when the NIH first issued its *Guidelines* to regulate the potential risks of laboratory conducted R-DNA research. Since that time the regulatory structure has expanded as a number of different federal agencies have used a variety of statutes to regulate biotechnology research and product development. One of the most controversial issues throughout the history of biotechnology regulation has been whether the regulation, on the one hand, is adequate to control the technology's risks, or, on the other hand, is unduly burdensome.[42]

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40. Although this concern focuses on genetic engineering, it could also apply to hybridization or traditional breeding techniques which mix plants and animals of different species.

41. Green, *supra* note 13, at 17. The Harris public opinion poll confirmed this observation. The poll found that thirty-five percent of those who think that genetic engineering of plants and animals is morally wrong believe this because they think that people have no business tampering with nature via R-DNA techniques. OTA, Report on Public Perceptions, *supra* note 31, at 58.

42. Numerous articles have discussed this question. *See, e.g.*, McGarity & Bayer, *Federal Regulation of Emerging Genetic Technologies*, 36 Vand. L. Rev. 461, 463 (1983) [hereinafter McGarity & Bayer]; Korwek & de la Cruz, *Federal Regulation of Environmental Releases of Genetically Manipulated Microorganisms*, 11 Rutgers Computer & Tech. L.J. 301 (1985); Karny, *Regulation of Genetic Engineering: Less Concern About Frankensteins but Time for Action on Commercial Production*, 12 U. Tol. L. Rev. 815 (1981) [hereinafter Karny, *Frankensteins*]; Hutt, *Research on Recombinant DNA Molecules: The Regulatory Issues*, 51 S. Cal. L. Rev. 1435 (1978) [hereinafter Hutt]; McChesney & Adler, *Biotechnology Released from the Lab: The Environmental Regulatory Framework*, 13 Envtl. L. Rep. 10,366 (1983); Naumann, *supra* note 11, at 62; Gore & Owens, *supra* note 15, at 336.

On the burdensome side, some even argue that such regulation infringes on the constitutional rights of scientists to conduct basic research. *See, e.g.*, Favre & McKinnon, *The New Prometheus: Will Scientific Inquiry Be Bound by the Chains of Government Regulation?*, 19 Duq. L. Rev. 651 (1981); Robertson, *The Scientist's Right to Research: A Constitutional Analysis*, 51 S. Cal. L. Rev. 1203 (1978). *But see* Barkstrom, *Recombinant DNA and the Regulation of Biotechnology: Reflections on the Asilomar Conference, Ten Years After*, 19 Akron L. Rev. 81, 107-09 (1985) (argues there is no such right) [herinafter Barkstrom]; Attanasio, *The Constitutionality of Regulating Human Genetic Engineering: When Procreation Liberty and Equal Opportunity Collide*, 53 U. Chi. L. Rev. 1274 (1986) (queries the constitutionality of possible government regulation of the distribution of biological abilities through genetic engineering); Fogleman, *Regulating Science: An Evaluation of the Regulation of Biotechnology Research*, 17 Envtl. L. Rep. 183, 185 (1987) (proposes regulating biotechnology research separately from technological products given the unique legal issues posed by the government regulation of science) [hereinafter Fogleman]. Most authors agree that even if there is a constitutional right to conduct scientific research, that right is far from absolute and can be infringed upon when the activity might jeopardize health, life, or property.

This section describes the historical development of the regulatory framework from its inception to the current proposals for reform, highlighting the controversies that have plagued, and in some cases, continue to plague, its evolution.

A. *The NIH Guidelines*

The NIH *Guidelines for Research Involving Recombinant DNA Molecules*[43] were issued in 1976 by the Recombinant DNA Advisory Committee (RAC)[44] within NIH and were to be applied to all NIH funded research.[45] The purpose of the *Guidelines* was to protect "the laboratory worker, the general public, and the environment from infection by possibly hazardous agents that [might] result from [R-DNA] research."[46]

As initially promulgated in 1976, the *Guidelines* reflected a cautious approach to the regulation of R-DNA.[47] Experiments fell into one of three groups: (1) prohibited, (2) exempt, or (3) requiring containment. Five types of experiments were specifically prohibited, including the deliberate release of genetically altered organisms into the environment.[48] Regulations for con-

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43. National Institutes of Health, *Guidelines for Research Involving Recombinant DNA Molecules*, 41 Fed. Reg. 27,906 (1976) [hereinafter *Guidelines*].

44. The RAC was established in 1974 by the Secretary of Health, Education and Welfare (now Health and Human Services) upon the recommendation of the Director of NIH. *See* Karny, *Frankensteins*, *supra* note 42, at 820.

45. The history of the development of the NIH *Guidelines* is probably best described by Swazey, Sorenson, and Wong. They recount the events and concerns that led researchers to call for a moratorium on certain types of R-DNA research in 1974, the efforts made by scientists to develop a consensus about how R-DNA research ought to proceed by forming an NIH Advisory Committee and by convening an international meeting at the Asilomar Conference Center in Pacific Grove, California, and the development and issuance of the NIH *Guidelines*. Swazey, Sorenson & Wong, *Risks and Benefits, Rights and Responsibilities: A History of the Recombinant DNA Research Controversy*, 51 S. CAL. L. REV. 1019 (1978).

46. Korwek, *The NIH Guidelines for Recombinant DNA Research and the Authority of FDA to Require Compliance with the Guidelines*, 21 JURIMETRICS J. 264, 268 (1981) [hereinafter Korwek, *The NIH Guidelines*]. The *Guidelines* have been both praised and criticized as a tool for the regulation of R-DNA research. Numerous legal questions have been raised about their adequacy and scope. In particular, several authors have asked whether the NIH *Guidelines* should extend to industry, whether NIH's RAC is an appropriate regulatory body, whether the RAC has the authority to enforce the *Guidelines*, and whether the *Guidelines* constitute administrative rules subject to the Administrative Procedure Act and to the National Environmental Policy Act. Several authors have indicated that, because of its role as a promoter of biomedical research, the NIH cannot be expected to be an aggressive regulator. *See, e.g.*, *id.* at 267; Gore & Owens, *supra* note 15, at 346; Naumann, *supra* note 11, at 65-70; Novick, *supra* note 3, at § 18.03[2]; Karny, *Frankensteins*, *supra* note 42, at 821, 840; Korwek, *Recombinant DNA and the Law: Review of Some General Legal Considerations*, 15 GENE. 1-5 (1981) [hereinafter Korwek, *Recombinant DNA and the Law*]; Hutt, *supra* note 42, at 1445.

47. *See* Isakoff, *supra* note 42, at 24; Naumann, *supra* note 11, at 65.

48. *Guidelines*, *supra* note 43, at 27,914-915. Other prohibited activities included: (1) the formation of recombinant DNA derived from certain pathogenic organisms; (2) the formation of R-DNA which contained genes that made vertebrate toxins; (3) the transfer of a drug resistant

tainment consisted of two types: physical and biological. These two types of containment were designed to prevent organisms from escaping from the laboratory and to prevent them from living long outside the lab if they did happen to escape. Varying levels of containment were required, depending on the level of risk associated with the activity.[49]

In addition to this technical framework, the *Guidelines* set forth an administrative framework for their implementation by specifying the roles and responsibilities of parties involved in the research.[50] Primary responsibility for particular experiments lay with the Principal Investigator (PI), the scientist receiving the funding. Specifically, the PI was responsible for determining the "real and potential biohazards of the proposed research" and for determining the appropriate level of biological and physical containment for the research.[51] Furthermore, each institution receiving NIH funds for R-

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trait to a microorganism that was not known to acquire it naturally if such acquisition could compromise the use of a drug to control disease agents in human or veterinary medicine or agriculture; (4) experiments using more than ten liters of culture unless the R-DNA was "rigorously characterized and the absence of harmful sequences established." *Id.*

49. The *Guidelines* specified four levels of physical containment designated Pl, P2, P3, and P4. The lowest level (Pl) coincided with the least risky situations and required the least restrictive laboratory practices and building designs. Korwek, *The NIH Guidelines*, *supra* note 46, at 268. At the highest risk level (P4), a "facility was to be engineered with 'monolithic walls,' air locks, double-door autoclaves for the sterilization and removal of waste, a separate negative pressure (inward) ventilation system, and Class-III Biological Safety Cabinets (enclosed cabinets with arm-length rubber gloves)." Barkstrom, *supra* note 42, at 90. The *Guidelines* further defined three levels of biological containment—EKl, EK2, and EK3—for different host-vector systems and different levels of risk. EK1 represented the lowest level of containment and EK3 the highest level. Most R-DNA experiments at the time were being performed with the bacterium *Escherichia coli* strain K-12, a generally benign bacterium. The use of this host bacterium, along with certain specified vectors, constituted the EK1 level of containment. The EK2 and EK3 levels required further modifications of the *E. coli* bacteria that made it more difficult for the bacteria to survive outside of the laboratory. For example, they might be modified so that they required certain nutrients which did not exist in significant concentrations in nature or so that they could not survive in sunlight. *See* Talbot, *Introduction to Recombinant DNA Research, Development and Evolution of the NIH Guidelines, and Proposed Legislation*, 12 U. TOL. L. REV. 804, 809 (1981) [herinafter Talbot]. The weakness of the biological containment system was that it applied exclusively to experiments performed on *E. coli.* Subsequently, the containment requirements were modified and renamed to reflect the fact that different organisms might be used in R-DNA experiments. Three levels—HV1, HV2, and HV3—were established specifically for experiments with host vectors other than *E. coli*, with HV1 providing for the least amount of restraint. Similarly, the physical containment categories were renamed and revised to reflect new knowledge regarding the risks of laboratory experiments. The new levels have been termed Biosafety Levels 1, 2, 3, and 4 (BL 1, 2, 3, and 4).

50. *See* Karny, *Frankensteins*, *supra* note 42, at 824; Barkstrom, *supra* note 42, at 89.

51. *Guidelines*, *supra* note 43, at 27,920. In addition, the PI was responsible for:

> selecting the microbiological practices and laboratory techniques for handling recombinant DNA materials, (iv) preparing procedures for dealing with accidental spills and overt personnel contamination, (v) determining the applicability of various precautionary medical practices, serological monitoring, and immunization, when available, (vi) securing approval of the proposed research prior to initiation of work, (vii)

DNA research was required to establish an institutional biosafety committee (IBC) to advise the institution on policies and ensure that the research was conducted in accordance with the *Guidelines*. The IBC was to provide a "quasi-independent review of [R-DNA] work done at the institution,"[52] reviewing, approving, and registering all proposed R-DNA experiments before their initiation and certifying that the containment standards were adequate.[53] The IBC was to be composed of individuals from the grantee institution or consultants, "selected so as to provide a diversity of disciplines relevant to recombinant DNA technology, biological safety, and engineering."[54]

The NIH was also responsible for making an independent evaluation of the real and potential biohazards of the proposed research and determining whether the proposed physical and biological containment safeguards certified by the IBC were appropriate to control the biohazards.[55] The approved safeguards were to be specified in a memorandum of understanding and agreement between NIH and the grantee.[56]

B. *Criticism of Early* Guidelines

Although, from a technical standpoint the *Guidelines* were thought to be a major achievement in the effort to control the physical and biological risks of R-DNA technology, from a legal standpoint the *Guidelines* were considered quite weak. Numerous authors felt that the only legal basis for

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submitting information on purported EK2 and EK3 systems to the NIH Recombinant DNA Molecule Program Advisory Committee and making the strains available to others, (viii) reporting to the institutional biohazards committee and the NIH Office of Recombinant DNA Activities new information bearing on the guidelines, such as technical information relating to hazards and new safety procedures or innovations, (ix) applying for approval from the NIH Recombinant DNA Molecule Program Advisory Committee for large scale experiments with recombinant DNAs known to make harmful products (*i.e.*, more than 10 liters of culture), and (x) applying to NIH for approval to lower containment levels when a cloned DNA recombinant derived from a shotgun experiment [was] rigorously characterized and there [was] sufficient evidence that it [was] free of harmful genes.

Id.

52. Karny, *Frankensteins*, *supra* note 42, at 825.
53. Korwek, *The NIH Guidelines*, *supra* note 46, at 269.
54. *Guidelines*, *supra* note 43, at 27,920.

In addition to possessing the professional competence necessary to assess and review specific activities and facilities, the committee [was to] possess or have available to it, the competence to determine the acceptability of its findings in terms of applicable laws, regulations, standards of practices, community attitudes, and health and environmental considerations . . . . The institution [was] responsible for reporting names of and relevant background information on the members of its biohazards committee to the NIH.

Id.

55. *Id.*
56. *Id.* at 27,921.

enforcement arose from contract law, that the *Guidelines* did not have the force of regulations.[57] Only institutions which received funds from NIH were covered by the *Guidelines*, and the only sanction that could be levied on those who did not comply was the loss of funds.[58]

A report issued by the Subcommittee on Investigations and Oversight of the House Committee on Science and Technology recognized this limitation of the *Guidelines* and cited others as well:

> Since their inception, the NIH Guidelines have been consistently criticized for three shortcomings. First, they are mandatory only for federally funded research; compliance by private companies is voluntary. Second, they do not apply to organisms created by genetic engineering methods other than recombinant DNA techniques. Finally, the Guidelines do not adequately address the issue of planned releases.[59]

Attempts were made to address at least the first of these shortcomings as early as 1976. In that year Senators Javits and Kennedy urged President Ford to explore every possible measure "for assuring that the NIH Guidelines would be adhered to" in all sectors of the research community.[60] In

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57. *See, e.g.*, Barkstrom, *supra* note 42, at 90; Korwek, *The NIH Guidelines*, *supra* note 46, at 267; Fogleman, *supra* note 42, at 205 and n. 119. The confusion over the legal basis of NIH's authority to enforce compliance with the *Guidelines* can be attributed to at least two factors: (1) when the original NIH *Guidelines* were promulgated, they did not include any statutory reference for their authority (this was partially remedied by the Draft Environmental Impact Statement which accompanied the *Guidelines*); (2) the *Guidelines* were adopted in accordance with informal rulemaking procedures making them appear to be administrative rules, having the force of law, apart from any contract. The problem with the argument that the *Guidelines* are actually rules lies with trying to find statutory authority for them. In attempting to find such authority, most have relied upon § 361 of the Public Health Service Act. Although § 361 authorizes the Department of Health and Human Services, NIH's umbrella agency, to "prevent the introduction, transmission, or spread of communicable diseases," Korwek and others have argued that this provision is not likely to apply to most genetically engineered organisms because such organisms do not generally involve the spread of communicable disease. *See* Korwek, *Recombinant DNA and the Law*, *supra* note 46, at 2. Korwek cites more convincing evidence of contract law as a basis for enforcement of the *Guidelines*. For example, the fact that the *Guidelines* originally required a memorandum of understanding and agreement between NIH and a grantee supports the contract argument. Moreover, the *Guidelines* specify required terms of funding and provide that NIH may "suspend, terminate or place other conditions upon the financing" of noncomplying projects. Karny, *Frankensteins*, *supra* note 42, at 825. In addition, in *Foundation on Economic Trends v. Heckler*, the D.C. Circuit held that "NIH approval of genetic engineering experiments is an explicit condition which must be satisfied before a scientist can receive federal funds for recombinant DNA research." Foundation on Economic Trends v. Heckler, 587 F. Supp. 753 (D.D.C. 1984) *aff'd in part, rev'd in part*, 756 F.2d 143 (D.C. Cir. 1985). Based on the case, Naumann asserts that the "courts may consider NIH's authority to be contractual in nature." Naumann, *supra* note 11, at 68.

58. Barkstrom, *supra* note 42, at 90.

59. SUBCOMMITTEE REPORT, *supra* note 14, at 7. *See also* Novick, *supra* note 3, at § 18.03[2]; McChesney & Adler, *supra* note 42, at 10,371.

60. Talbot, *supra* note 49, at 810 (quoting letter from Senators Javits and Kennedy to President Gerald R. Ford (July 1976)).

1977 the Federal Interagency Advisory Committee on Recombinant DNA Research[61] concluded that "none of the existing statutes completely answered the specific problems posed by recombinant DNA research,"[62] and recommended new national legislation to extend the NIH *Guidelines* by law to private industry.[63] Several bills were introduced in Congress that year to address these issues, but none were passed.[64]

C. *Revisions to the* Guidelines

In December 1978 NIH issued revised *Guidelines*[65] accompanied by an environmental impact assessment. The new *Guidelines* were a relaxation of the earlier standards. For example, "experiments were assigned lower levels of required containment; [and] classes of experiments deemed of the lowest potential hazard were exempted entirely from the Guidelines."[66] The *Guidelines* were also revised to allow releases of genetically altered organisms into the environment on a case-by-case basis. Up until that time such releases had been prohibited.[67]

In addition, the RAC was expanded from sixteen members, who were primarily scientists, to twenty-five members that included "persons knowledgeable in applicable law, standards of professional conduct and practice, public attitudes, the environment, public health, occupational health, or related fields."[68] The purpose of the expansion was to increase public participation in the decisionmaking process.

Finally, the 1978 revisions incorporated a process for future changes to the *Guidelines* consisting of notice in the Federal Register and an opportunity for public comment.[69] Since that time the *Guidelines* have been incrementally modified in this fashion on a regular basis.

At least three significant revisions were made to the *Guidelines* in 1980. First, the *Guidelines* eliminated the need for a memorandum of understanding and agreement (MUA) between the grantee and the NIH. The MUA had

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61. The advisory committee was created in 1976 and consisted of members from eighteen federal agencies that either funded or could potentially regulate R-DNA research. *See* Talbot, *supra* note 49, at 810.

62. Barkstrom, *supra* note 42, at 92.

63. Talbot, *supra* note 49, at 810.

64. *See id.* and Barkstrom, *supra* note 42, at 92 for a detailed description of the congressional activity. Some have speculated that the reason for the lack of congressional action was the accumulation of scientific evidence that R-DNA research was basically a safe activity. *See* Barkstrom, *supra* note 42, at 93.

65. National Institutes of Health, *Guidelines for Research Involving Recombinant DNA Molecules*, 43 Fed. Reg. 60,080 (1978).

66. Talbot, *supra* note 49, at 812.

67. 43 Fed. Reg. 60,126 (1978). Deliberate releases remained in the prohibited category but the prohibition could be waived with RAC approval.

68. *Id.* at 60,081.

69. *Id.* at 60,080.

provided detailed information about each experiment and "was the institution's certification to the NIH that the experiment had complied with the Guidelines."[70] Under the revised *Guidelines* the only type of monitoring required was that "the institution, IBC or PI notify [the NIH] of any significant violations, accidents, or problems with interpretation."[71] Second, in 1980 the NIH promulgated physical containment recommendations for large scale uses of organisms containing recombinant DNA molecules.[72] These recommendations were intended to serve as a guide to private companies which engaged in large-scale R-DNA experiments.[73] The recommendations categorized large-scale projects according to the expected level of risk. Just as they were able to ignore the *Guidelines* themselves, however, private companies were also able to ignore these recommendations.[74] In order to encourage use of the *Guidelines* by industry, in 1980 the NIH also provided a means for voluntary compliance.[75] In exchange for voluntary compliance, the NIH would protect all proprietary information voluntarily submitted.[76]

In 1981 the NIH proposed a radical change that would have made compliance with the *Guidelines* totally voluntary.[77] Institutions would not be required to establish IBCs or to obtain IBC or RAC approval prior to initiating R-DNA research.[78] In response to significant criticism, the NIH reversed its position in the proposal and issued a second proposal that "exempted many more activities from RAC scrutiny," but required that NIH funded institutions continue to establish IBCs and comply with the *Guidelines*.[79] Deliberate release experiments were removed from the "prohibited" category and were permitted with RAC review and approval by the NIH and the institution's IBC.[80] Also, in 1981 the RAC approved the first deliberate release experiment—a genetically engineered corn plant. In 1983 the RAC approved two additional field tests, "one involving recombinant DNA-de-

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70. Karny, *Frankensteins*, *supra* note 42, at 834.

71. *Id.* at 835.

72. *Recombinant DNA Research: Physical Containment Recommendations for Large-Scale Uses of Organisms Combining Recombinant DNA Molecules*, 45 Fed. Reg. 24,968 (1980).

73. In the original *Guidelines* most large scale experiments, *i.e.*, those involving more than ten liters of R-DNA bacteria culture, were prohibited. Although a number of companies, not covered by the *Guidelines*, wished to conduct large-scale research, there were no *Guidelines* available for large-scale work.

74. *See* McGarity & Bayer, *supra* note 42, at 502.

75. *Research Involving Recombinant DNA Molecules: Guidelines*, 45 Fed. Reg. 77,404 (1980).

76. *Id.*

77. *See* J. GIBBS, I. COOPER & B. MACKLER, BIOTECHNOLOGY AND THE ENVIRONMENT: INTERNATIONAL REGULATION 103 (1987) [hereinafter J. GIBBS].

78.. *Recombinant DNA Research: Proposed Revised Guidelines*, 46 Fed. Reg. 59,368 (1981).

79. J. GIBBS, *supra* note 77, at 103.

80. *Recombinant DNA Research: Proposed Actions Under Guidelines*, 50 Fed. Reg. 33,462 (1985).

rived tomato and tobacco plants and one involving 'ice minus,' a microbe which inhibits frost formation."[81]

The lifting of the ban against deliberate releases shifted the focus of the RAC from a monitor of laboratory safety to an evaluator of deliberate release experiments.[82] The approval by NIH of the three deliberate release experiments "refueled public debate over r-DNA research and provoked the first court challenge to the administration of the NIH Guidelines . . . ."[83]

In 1984 a complete revision of the *Guidelines* appeared in the Federal Register.[84] The 1984 *Guidelines* were significantly less stringent than those initially published in 1976. There were no prohibited experiments; instead experiments fell into one of four categories: (1) those requiring both IBC and RAC approval; (2) those requiring only IBC approval; (3) those requiring only IBC notification; and (4) those which were exempt.[85] By 1984 most experiments fell into categories (3) and (4) and only four types of experiments required approval from both the IBC and the RAC.[86] Deliberate releases were numbered among the four types of experiments requiring dual approval.[87]

Despite the early criticisms, by 1984 there was considerable acceptance of the NIH *Guidelines* and revisions, primarily due to their flexibility and fluidity.[88] At the same time, however, the NIH *Guidelines* were beginning to lose their role as the primary regulatory mechanism for biotechnology activity.

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81. *See* SUBCOMMITTEE REPORT, *supra* note 14, at 5.

82. *See* Gore & Owens, *supra* note 15, at 345. In 1984 there was a significant increase in the number and diversity of proposals submitted to NIH and other government agencies to release genetically engineered organisms into the environment. These proposals "included organisms ranging from plants genetically-engineered to be herbicides or disease-resistant, to genetically-engineered microbial pesticides." SUBCOMMITTEE REPORT, *supra* note 14, at 5.

83. Note, *Rutabaga*, *supra* note 15, at 1537. In *Foundation on Economic Trends v. Heckler*, 756 F.2d 143 (D.C. Cir. 1985), the plaintiffs, led by Jeremy Rifkin, sought an injunction against the approval of an experiment involving the spraying of ice inhibiting bacteria on a potato field.

84. *Guidelines for Research Involving Recombinant DNA Molecules*, 49 Fed. Reg. 46,266-91 (1984).

85. J. GIBBS, *supra* note 77, at 104.

86. *Id.*

87. Other experiments requiring approval of both the RAC and the institution's IBC are: (1) "deliberate formation of rDNA-containing genes for toxic molecules with an LD50 for vertebrates of less than 100 nanograms per kilogram of body weight"; (2) "deliberately transferring a drug resistance trait to microorganisms that naturally lack that trait, if the transfer could 'compromise the use of the drug to control disease agents in human or veterinary medicine or agriculture' "; and (3) "deliberately transferring rDNA, or DNA or RNA derived from rDNA, into human beings." *Guidelines for Research Involving Recombinant DNA Molecules*, 51 Fed. Reg. 16,960 (1986).

88. *See* Novick, *supra* note 3, at § 18.03[2] ("[The NIH *Guidelines]* have been and remain enormously influential."); McGarity & Bayer, *supra* note 42, at 501 ("The Guidelines have received broad support and have served as a model for regulators throughout the world.").

IV. Statutory Mechanisms for Regulation of Biotechnology

Between 1977 and 1984 it became clear that a new statute specifically designed to regulate biotechnology was not forthcoming. During that time scientists, lawyers, and environmentalists debated whether existing public health, agriculture, and environmental statutes could sufficiently regulate biotechnology activity.[89] Over a dozen statutes were cited as potentially applicable to commercial biotechnology activities, although no statute at the time explicitly mentioned biotechnology.[90] This section discusses the pre-1984 statutes, regulations, and agency practices that were relevant to biotechnology and explores the adequacy of these statutes, regulations, and practices.

A. *Environmental Statutes*

1. *FIFRA*

The Environmental Protection Agency has relied chiefly on two statutes as a basis for the regulation of biotechnology activities: the Federal Insecticide, Fungicide and Rodenticide Act[91] (FIFRA) and the Toxic Substances Control Act[92] (TSCA).

FIFRA provides authority for the regulation of products such as chemicals and microorganisms intended for use as pesticides. The statute was thought to be particularly relevant to the biotechnology industry, whose spokespersons predicted that "within the next 20 years, biotechnology products [would] capture the 'lion's share' of the agricultural and consumer pesticides market."[93] FIFRA defines a pesticide broadly as "any substance or

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89. *See, e.g.*, McChesney & Adler, *supra* note 42.

90. These statutes include: Toxic Substances Control Act (TSCA), 15 U.S.C. §§ 2601-29 (1982); Federal Food, Drug and Cosmetic Act (FDCA), 21 U.S.C. §§ 301-92 (1982); Public Health Services Act (PHS), 42 U.S.C. §§ 262-63 (1982); Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), 7 U.S.C. §§ 136-136y (1982); Occupational Safety and Health Act (OSHA), 29 U.S.C. §§ 651-78 (1982); Clean Water Act (CWA), 33 U.S.C. §§ 466-466g (1982); Resource Conservation and Recovery Act (RCRA), 49 U.S.C. §§ 6901-87 (1982); Federal Clean Air Act (CAA), 42 U.S.C. §§ 7401-7642 (1982); Federal Meat Inspection Act (FMIA), 21 U.S.C. §§ 601-95 (1982); Poultry Products Inspection Act (PPIA), 7 U.S.C. §§ 1621-30 (1982); Virus, Serum and Toxin Act (VSTA), 21 U.S.C. §§ 151-58 (1982); National Environmental Policy Act (NEPA), 42 U.S.C. §§ 4321-70 (1982); Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), 42 U.S.C. §§ 9601-57 (1982); Noxious Weed Act (NWA), 7 U.S.C. §§ 2801-13 (1988); Plant Pest and Plant Quarantine Acts (PPPQA), 7 U.S.C. §§ 150aa-150jj (1982); Plant Quarantine Act (PQA), 7 U.S.C. §§ 151-67 (1982); Endangered Species Act (ESA), 16 U.S.C. §§ 1531-43 (1982). Many authors pointed out the shortcomings of each of these statutes for the regulation of biotechnology and the failure of the agencies involved to address biotechnology directly.

91. Federal Insecticide, Fungicide and Rodenticide Act, 7 U.S.C. §§ 136-136y (1982).

92. Toxic Control Substances Act, 15 U.S.C. §§ 2601-54 (1982).

93. Kriz, *Growing Biotechnology Industry Sparks Governmental Turf Battle over Fed-*

mixture of substances intended for preventing, destroying, repelling or mitigating any pest or intended for use as a plant regulator, defoliant or desiccant."[94] Historically, most of the regulated pesticides have been chemical substances, but in the 1970s and early 1980s, microbial pesticides were becoming more commonplace. In 1979 the EPA established an official policy to regulate living organisms intended for use as pesticides on the basis that such organisms were "biological control agents" and as such were "substances" subject to regulation.[95] In 1982 the EPA announced that some biotechnology products, particularly genetically engineered microorganisms, would be covered under this policy,[96] and in 1984 it published pesticide assessment guidelines for microbial pesticides.[97] Some authors speculated that because FIFRA defined "pesticide" as a "substance," EPA regulation of living organisms might be subject to legal challenge, but no such challenge has yet taken place.[98]

FIFRA requires all pesticide manufacturers to register their pesticides with the EPA before marketing them in interstate commerce, and conditions registration on the performance of tests and submission of data concerning the product's safety and efficacy.[99] If the EPA determines that a pesticide might cause unreasonable adverse effects to the environment, including injury to applicators, pesticide registrations may be restricted to particular uses. Prior to 1984 the data required to accompany an application for registration "primarily concerned direct toxicity effects upon various animal species."[100] These limited requirements were criticized by some, as they left open the possibility of approval of organisms with a variety of indirect effects that could be ecologically damaging.[101]

In order to obtain the data necessary to complete a registration application, manufacturers were often required to perform small and large scale field tests in addition to laboratory experiments. Prior to conducting such field tests, a manufacturer was frequently required to obtain an experimen-

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eral Regulation of Potential Health and Environmental Risks, 8 CHEM. REG. REP. 393, 395 (1984).

94. 7 U.S.C. § 136 (1982).

95. 44 Fed. Reg. 23,994 (1979).

96. *See Pesticides Registration: Proposed Data Requirements* 47 Fed. Reg. 53,192, 53,203 (1982). The EPA also recognized, however, that both the USDA and the Department of the Interior had regulatory jurisdiction over living organisms and, in deference to these agencies, exempted all living organisms from its oversight as pesticides except viruses, bacteria, protozoa, fungi, and certain unicellular plants. 40 C.F.R. § 162.5(c)(1)(i) & (ii), (c)(4)(i)-(v) (1988).

97. The *Guidelines* specified the standards for conducting acceptable tests, and provided guidance on evaluation and reporting of data, further guidance on when data were required, and examples of recommended testing protocols. *See Proposal for a Coordinated Framework for Regulation of Biotechnology*, 49 Fed. Reg. 50,856, 50,882 (1984).

98. *See* McChesney & Adler, *supra* note 42, at 10,374-75.

99. *Id.* at 10,374.

100. *Id.* at 10,375.

101. *Id.*

tal use permit (EUP) from the EPA.[102] The EUP allowed an applicant to bypass the lengthy delays and expense of registration in the early development of a pesticide. In applying for an EUP, a manufacturer was required to describe "among other items, the objectives of the test, the proposed testing program, the amount of pesticide involved, the results of prior tests with the pesticide . . . and the proposed method of storage and disposition."[103]

Prior to 1984 an EUP was not needed for "small-scale" field tests—*i.e.*, field tests conducted on no more than ten acres of land or no more than one surface acre of water[104]—"so long as the principal purpose of the test [was] to establish the pesticide's effectiveness, rather than to provide actual pest control."[105] This exemption prompted some criticism of FIFRA as failing to provide appropriate control over microorganisms—particularly genetically altered microorganisms. Critics argued that "with viable pesticides, the difference between 100 square feet and 10 acres is not really a matter of scale but a matter of time." A microbial pesticide may multiply to "ten acres in a few hours or days."[106]

2. *Toxic Substances Control Act*

In addition to FIFRA, the Toxic Substances Control Act (TSCA)[107] was frequently cited as a source of authority for the regulation of the release of genetically engineered organisms into the environment.[108] TSCA was enacted by Congress in 1976 "to provide a comprehensive mechanism for gathering data on the health and environmental effects of chemical substances, for assessing the risks of these substances, and for ensuring that the manufacture, distribution, use and disposal of toxic materials [did] not pose unreasonable risks to man and the environment."[109] Experts cited three key mechanisms that could be used by the EPA to regulate genetically engineered organisms under TSCA. These included the premanufacture notification (PMN) provision, the significant new use rules (SNUR), and the data reporting requirements. The most important of these was the PMN provision.

Under section 5 of the Act, any person who intends to manufacture or import a "new" chemical substance for commercial purposes into the United States must submit a PMN to the EPA at least 90 days prior to manufacture. A "new" chemical substance is one that does not appear on the TSCA

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102. *See* 7 U.S.C. § 136c (1982).
103. J. GIBBS, *supra* note 77, at 14.
104. 40 C.F.R. § 172.3 (1988).
105. Note, *Rutabaga*, *supra* note 15, at 1545.
106. Panem, *supra* note 3, at 5.
107. Toxic Substances Control Act, 15 U.S.C. §§ 2601-54 (1982).
108. *See 1984 Proposal for Regulation of Biotechnology*, 49 Fed. Reg. 50,886 (1984).
109. McGarity & Bayer, *supra* note 42, at 505.

Chemical Substance Inventory and that is not "naturally occurring."[110] The notice, which consists of a form prepared by the EPA, must contain "certain descriptive information, test data that are in the manufacturer's possession, and any other data on health or environmental effects known to or reasonably ascertainable by the manufacturer."[111] During the ninety-day period, the EPA staff first reviews the information to determine whether there is sufficient data to make an adequate assessment of risk. If there is not, the agency may request additional information from the manufacturer. Once the EPA is satisfied that it has the data it needs, the agency begins its substantive review. If the EPA has a reasonable basis to conclude that commercial use of the substance will present an unreasonable risk, it can prohibit its manufacture, but only by obtaining a court order under section 5(e) of the Act. If the EPA does not take action on a substance within the ninety-day review period, the substance is added to the Chemical Substance Inventory.

In the late 1970s and early 1980s several shortcomings of the PMN process became evident which raised questions about the adequacy of TSCA to regulate genetically engineered organisms. For example, the process does not limit the uses of an "approved" chemical to those uses specified in the PMN. Thus, once a chemical substance is in the TSCA inventory, it can be used for any purpose. TSCA does, however, include a provision which allows the EPA to promulgate a significant new use rule. The rule typically requires that a manufacturer notify the EPA of a new use; it may require that the substance be subject to PMN review prior to the new use.[112]

Finally, TSCA includes an information-gathering provision which numerous authors referred to as a major strength in the regulation of the products of biotechnology.[113] Under section 8(a) of the Act, the EPA has the authority "to require the testing of chemicals, the retention of reports of significant allegations of adverse reactions to health or the environment, the report of available health studies on chemicals and the report of information which supports the conclusion that chemicals present substantial risks of injury to health or the environment."[114]

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110. *See* 40 C.F.R. §§ 720.25, 720.30(h) (1988).

111. Novick, *supra* note 3, at § 18.03[5][d][ii][a].

112. *Id.* at § 18.03[5][d][ii][c].

113. *See, e.g.*, McGarity & Bayer, *supra* note 42, at 510 (discussing the use of the data gathering provision of TSCA in regulating genetically engineered organisms).

114. Novick, *supra* note 3, at § 18.03[5][d][ii][b]. In addition to these three key provisions, under § 4 of TSCA, the EPA may require manufacturers or processors of chemicals to test the toxic effects of substances they produce if the agency finds that the chemical may present an unreasonable risk of injury to health or the environment; that there are insufficient data available with which to reasonably determine or predict the effects of the chemical; and that testing is necessary to generate such data. *See* 15 U.S.C. § 2603(a) (1982). Also, § 6 of the Act permits the EPA to prohibit or limit the amount of a substance which may be manufactured, processed, or distributed in commerce for a particular use; require labeling of or retention of records of the processes used to manufacture or process chemical substances; or impose quality control procedures. *See* 15 U.S.C. § 2605(a) (1982). Regulation under § 6, however, re-

The major debate with respect to the use of TSCA to regulate genetically engineered organisms was whether such organisms were covered under the statute. Several authors questioned the applicability of TSCA to live organisms.[115] Most remarked that whether TSCA covers intentional releases or commercial uses of genetically altered organisms depends on whether such organisms are "chemical substances" or "mixtures."[116] Neither the statutory definitions nor the legislative history of these terms specifically mentioned living organisms. Moreover, when Congress passed the Act in 1976, it probably "never considered the nascent biotechnology industry."[117] Yet some authors have argued that "the tendency of the courts to construe the environmental statutes broadly in order to achieve their remedial purpose [might] allow extension of TSCA to biotechnology products."[118]

The EPA has also changed its position on the applicability of TSCA to live organisms. Although at one time the EPA took the position that "genetically engineered microorganisms were not within the ambit of TSCA's statutory definition of chemical substances," it later reversed itself, stating that "TSCA's definition of chemical substances encompasses both naturally occurring and genetically engineered living microorganisms, as well as the chemical products produced by such organisms."[119] Several authors stated that the legal validity of this position was uncertain, and a congressional report concluded that it was "not unlikely that EPA's authority [in this regard might] be challenged in court."[120]

The EPA argued that TSCA's legislative history provides evidence that

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quires the EPA to possess a reasonable basis for believing that a substance presents or will present an unreasonable risk of harm. *See* 40 C.F.R. § 750 (1987).

115. *See, e.g.*, McGarity & Bayer, *supra* note 42, at 505-06; McChesney & Adler, *supra* note 42, at 10,373; Note, *Biotechnology Regulation Under the Toxic Substances Control Act*, 3 PACE ENVTL. L. REV. 57 (1985) [hereinafter Note, *Biotechnology Regulation Under TSCA*]; Shiffbauer, *Regulating Genetically Engineered Microbial Products Under the Toxic Substances Control Act*, 15 ENVTL. L. REP. 10,279, 10,281 (1985); Barkstrom, *supra* note 42, at 93; Note, *Rutabaga*, *supra* note 15, at 1546; Gore & Owens, *supra* note 15, at 347; Harlow, *The EPA and Biotechnology Regulation: Coping with Scientific Uncertainty*, 95 YALE L.J. 563 (1986); Naumann, *supra* note 11, at 74.

116. *See, e.g.*, McChesney & Adler, *supra* note 42, at 10,373; Note, *Rutabaga*, *supra* note 15, at 1546.

117. McChesney & Adler, *supra* note 42, at 10,374.

118. *Id.*

119. Note, *Biotechnology Regulation Under TSCA*, *supra* note 115, at 65 (quoting from a letter from Douglas M. Costle, EPA Administrator, to Senator Adlai E. Stevenson, III, Chairman, Subcomm. on Science, Technology, and Space, U.S. Senate Comm. on Commerce, Science, and Transportation (Dec. 9, 1977)). The term chemical substance is defined as: "any organic or inorganic substance of a particular molecular identity, including—(i) any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature, and (ii) any element or uncombined radical." 15 U.S.C. § 2602(2)(B) (1982).

120. *See* SUBCOMM. ON INVESTIGATIONS AND OVERSIGHT, HOUSE COMM. ON SCIENCE AND TECHNOLOGY, 98TH CONG., 2D SESS., REPORT ON THE ENVIRONMENTAL IMPLICATIONS OF GENETIC ENGINEERING (Comm. Print 1984).

TSCA is a "gap-filling" statute—*i.e.*, it was "intended to provide authority over substances not covered by other health and environmental laws" and therefore extends "jurisdiction of the Act to microbial products of biotechnology as a statute of last resort."[121] At least one author argued that such an interpretation might be "overly-broad."[122]

In addition to the question of whether TSCA could be used at all to regulate whole organisms, several other weaknesses of the statute as a basis for regulating genetically engineered organisms were pointed out *prior* to 1984. Among the specific concerns raised were the following:

1. The PMN only requires that a manufacturer submit health and safety data which he has in his possession or control.[123] Environmentalists argued that the EPA might not have adequate information to assess the risks of a new genetically engineered organism. Although the EPA could require additional tests via its data gathering authority, it rarely invoked this authority.[124]

2. The PMN program is "not a permit system; it merely affords the EPA notice and opportunity for review."[125] The EPA has the burden of reviewing and taking action to halt production of a chemical substance within a ninety-day period—"[u]nless EPA vigorously pursues its opportunities under [the PMN provision], products can legally go to the marketplace un-

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121. Shiffbauer, *supra* note 115, at 10,282.

122. *Id. See also* J. GIBBS, *supra* note 77, at 36. At least three congressmen were concerned enough about the ability of the EPA to use TSCA to regulate genetically altered organisms that they introduced legislation to address the issue. Between 1983 and 1985 both Senator Durenberger and Representative Florio introduced legislation that would have explicitly allowed the EPA to regulate genetically engineered organisms under TSCA. See S. 1967, 99th Cong., 1st Sess. (1985) (reprinted in 5 Biotech. L. Rep. 92 (Mar. 1986)); H.R. 4303 and H.R. 4304, 98th Cong., 1st Sess. (1983). The bills did not pass.

123. *See* Novick, *supra* note 3, at § 18.03[5][d][ii][a]. According to Korwek, criticism of PMN information requirements overlooks the fact that under § 5(e) of TSCA, the EPA may request additional data if:

> (1) the information available in a PMN submission or from other sources is insufficient to determine the health and environmental effects of a substance and; (2) the manufacture, processing, distribution, use or disposal of the substance, or any combination of such activities, *may* present an unreasonable risk of injury to the health of the environment; (3) the substance is produced in substantial quantities and *may* reasonably be anticipated to enter the environment in such quantities; or (4) there *may* be significant or substantial human exposure.

Korwek, *Implications of TSCA: Emerging Roles of NIH and EPA in the Regulation of rDNA Technology*, 1 BIOTECHNOLOGY 757 (Nov. 1983) [hereinafter Korwek, *Emerging Roles of NIH and EPA*].

124. Environmentalists argued that historically the EPA rarely used the procedurally complex and burdensome 5(e) order. Between July 1979 and March 1983, the EPA received 2201 PMNs and issued 7 § 5(e) orders. During that time, however, the agency obtained 49 voluntary control agreements and 9 PMNs were withdrawn in the face of 5(e) orders. *See* J. GIBBS, *supra* note 77, at 42.

125. Novick, *supra* note 3, at § 18.03[5][e].

reviewed."[126] Furthermore, in order to prevent production, the EPA is required to obtain a court order under section 5(e) of the Act, a "procedurally complex and labor intensive" effort.[127]

3. Under most provisions of TSCA, the use of a chemical substance may be regulated only if its use presents an "unreasonable risk" of injury to health or the environment.[128] Although "unreasonable risk" is not defined in the statute, the legislative history makes "it clear that the determination involves an analysis of the risk posed by a substance, which encompasses a consideration of the probability of harm based upon exposure and severity, and a balancing of the risks and benefits to society."[129]

4. The PMN only applies to "new substances," and although the EPA can establish a SNUR for new "uses," it uses the SNUR provision sparingly.[130]

5. There is a significant loophole in the PMN process: small quantities of chemicals used for research and development are generally exempt from PMN review.[131] In addition, the PMN requirements do not apply to any non-commercial research and development, *i.e.*, research sponsored and conducted by an academic or other non-profit institution. The exemption does not apply, however, if the research is funded by industry or intended to culminate in a commercial product.[132]

B. *Other Statutes Under the EPA's Jurisdiction*

A number of other environmental statutes were also evaluated as a means of regulating biotechnology research and product development. For example, the Clean Air and Clean Water Acts were discussed as possible sources of authority for EPA regulation of release of genetically altered organisms into the environment.[133] Of these two, the Clean Water Act (CWA)

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126. *Id.*

127. *Id.* at § 18.03[5][d][iv]. *See supra* notes 123, 124 for a more detailed discussion of the use of § 5(e) orders.

128. Barkstrom, *supra* note 42, at 93.

129. KORWEK, 1988 BIOTECHNOLOGY REGULATIONS HANDBOOK 121 (1988) (relying on legislative history of TSCA) [hereinafter KORWEK, 1988 BIOTECHNOLOGY REGULATIONS].

130. According to Gibbs, as of 1986 the EPA had promulgated SNURs for only twelve chemicals. J. GIBBS, *supra* note 77, at 39-40.

131. *See* 15 U.S.C. § 2604(h)(3) (1982). "Small quantities" has been defined by the EPA as amounts manufactured "solely for R&D that are not greater than reasonably necessary for such purposes." 40 C.F.R. § 720.3(cc) (1988). Korwek has argued that this is not a serious loophole, but rather a desirable one, because the estimated cost of submitting a PMN is very high. In 1983 it ranged from $5,800 to $14,000. These costs, he argues, "could easily chill scientific research at university laboratories and inhibit technological innovation. Finally, and perhaps more importantly, genetic R&D is not excluded from regulation under other provisions of TSCA [specifically, §§ 4 and 6] and commercial applications are still subject to PMN." Korwek, *Emerging Roles of NIH and EPA*, *supra* note 123, at 757.

132. *See* J. GIBBS, *supra* note 77, at 40.

133. *See* Korwek & de la Cruz, *supra* note 42, at 376-80; Novick, *supra* note 3, at §

was thought to be the more useful for regulating bioengineered organisms. The CWA prohibits the discharge of pollutants, including biological materials,[134] from point sources into the nation's surface waters without a federal National Pollution Discharge Elimination System (NPDES) permit or a comparable state permit.[135] Most biotechnology companies, including those that manufacture foods, drugs, and biologics, generate wastes that could conceivably subject them to CWA.[136]

The Clean Air Act (CAA), though mentioned as a possible source of regulatory authority, was thought to be a somewhat ineffective and cumbersome mechanism for this purpose.[137] Although the definition of "air pollutants"[138] is broad enough to encompass biotechnological substances,[139] the structure and enforcement of CAA make it unlikely to apply to genetically altered organisms.[140]

18.03[6]; McChesney & Adler, *supra* note 42, at 10,375; McGarity & Bayer, *supra* note 42, at 507.

134. 33 U.S.C. § 1362(6) (1982).

135. 33 U.S.C. § 1342(k) (1982).

136. Although the CWA could provide useful authority for the regulation of genetically engineered organisms, it also has several shortcomings that would limit its effectiveness in this regard. For example, the NPDES permit requires compliance with national effluent limitations promulgated by the EPA for specified categories of industries, "based on the effectiveness and cost of control technologies available for those industries." McChesney & Adler, *supra* note 42, at 10,375. In addition to the technology-based standards, the CWA authorizes states to set effluent limitations as part of water quality standards. 33 U.S.C. § 1313(a)(2) (1982). Although the CWA authorizes states to set water quality standards for biological pollutants, "the state-administered water quality standards have not played a large role in controlling water pollution." Novick, *supra* note 3, at § 18.03[6][b].

Korwek and de la Cruz pointed out that the NPDES permit program was "designed to limit the release of pollutants from sources that discharge waste water on a regular or periodic basis. As such it would be ill-suited as a regulatory tool to govern deliberate releases." Korwek & de la Cruz, *supra* note 42, at 380. This criticism, however, appears to overlook the fact that there may be biotechnology companies, *e.g.*, pharmaceutical companies or those that utilize fermentation techniques, that will generate waste water on a regular basis. These companies would be subject to the technology-based effluent standards established for pharmaceutical companies and any relevant state water quality standards.

137. Korwek & de la Cruz, *supra* note 42, at 348.

138. "Air pollutants" is defined to mean "any air pollution or agent or combination of such agents, including any physical, chemical, biological . . . substance or matter which is emitted into or otherwise enters the ambient air." 42 U.S.C. § 7602(g) (1982).

139. Korwek & de la Cruz, *supra* note 42, at 329.

140. *Id.* at 330. The Clean Air Act regulates two major categories of pollutant air emission from existing stationary sources: (1) so-called "criteria" pollutants—those that may reasonably be expected to endanger public health or welfare, and (2) hazardous pollutants. The currently listed criteria pollutants are sulfur dioxide, particulate matter, carbon monoxide, ozone, nitrogen dioxide, and lead. 40 C.F.R. § 50 (1988). The currently listed hazardous air pollutants are asbestos, benzene, beryllium, coke oven emissions, inorganic arsenic, mercury, radionuclides, and vinyl chloride. 40 C.F.R. § 61 (1988).

The CAA regulates criteria pollutants by calling for the establishment of national ambient air quality standards (NAAQS) which are largely enforced through state implementation plans.

In addition to CAA and CWA, the statutes regulating hazardous waste were mentioned as possible sources of regulatory authority for controlling the release of genetically engineered organisms[141]—specifically, the Resource Conservation and Recovery Act (RCRA)[142] and the Comprehensive Environmental Response Compensation and Liability Act (CERCLA)[143] or Superfund. RCRA provides a comprehensive framework for the regulation of hazardous waste from generation to disposal.[144] Hazardous wastes are defined as wastes which, because of their "quantity, concentration, or physical, chemical or infectious characteristics," are toxic or which "otherwise cause a substantial hazard to health or the environment when improperly managed."[145] The definition indicated that "hazards to the environment, as well as to health, [could] lead to regulation of wastes, and the inclusion of 'infectious' characteristics plainly evidence[d] an intent to include living organisms . . . ."[146] The EPA, however, has not included living organisms among the wastes to be regulated under RCRA.[147]

The EPA also has the authority to set standards for new sources of pollutants (new source performance standards) and hazardous air pollutants under the National Emission Standards for Hazardous Air Pollutants (NESHAPS). 42 U.S.C. § 7411 (1982). The NAAQS may be set to protect either the public health or welfare, 42 U.S.C. § 7409(b)(1)-(2) (1982), "but practically speaking only the health-based . . . standards are enforceable." Novick, *supra* note 3, at § 18.03[6][a]. Several sources stated that bioengineered organisms would not be emitted in significant enough quantities to be the subject of NAAQS. *Id. See also* McGarity & Bayer, *supra* note 42, at 507, stating that "[i]n the normal operation of a fermentation plant or large-scale release process the chances are remote that significant emissions of current criteria [pollutants]. . .will result unless a laboratory decides to dry liquid wastes and incinerate them." Furthermore, "organisms containing rDNA molecules probably [would] not qualify as new criteria pollutants because plants [would] not release them from 'numerous or diverse mobile or stationary sources'—a necessary precondition." *Id.* Nor was the NESHAPS program thought to be a likely regulatory tool "since very few, if any, of the organisms scheduled for deliberate release would be expected to have significant impacts on human health." Novick, *supra* note 3, at § 18.03[6][a]. One possible exception cited was the release of human pathogens from a production facility, but according to Novick, "such releases were not likely to be of a large enough magnitude to justify imposition of a national standard." *Id.*

141. *See, e.g.*, McGarity & Bayer, *supra* note 42, at 508; Korwek & de la Cruz, *supra* note 42, at 367; McChesney & Adler, *supra* note 42, at 10,378; Novick, *supra* note 3, at § 18.04.

142. 42 U.S.C. §§ 6901-87 (1982).

143. 42 U.S.C. §§ 9601-57 (1982).

144. Novick, *supra* note 3, at § 18.04[2].

145. *Id.*

146. *Id.*

147. Korwek and de la Cruz pointed out that the RCRA could come into play in the regulation of deliberate releases if genetically manipulated organisms were used to treat hazardous waste. "If a facility intends to conduct biological treatment of hazardous waste, it must: obtain an identification number from [the] EPA; conduct a general waste analysis; provide for security, ground-water monitoring, and proper storage and treatment facilities; meet certain financial requirements; and develop contingency and emergency procedures." Korwek & de la Cruz, *supra* note 42, at 370. The authors commented that while genetically-manipulated organisms might not be deemed solid or hazardous waste, their use in hazardous waste treatment might subject them to RCRA regulation. *Id.* at 371. They concluded, however, that "[o]verall,

Others argued that CERCLA "could prove to be an important source of legal authority if releases of products of biotechnology posed health or environmental threats warranting cleanup."[148] CERCLA provides for the expeditious cleanup of hazardous substances or pollutants that threaten the environment. Specifically, the EPA is authorized to respond to a "release (or substantial threat of a release) of a 'hazardous substance' or to an imminent hazard posed by a 'pollutant or contaminant.' "[149] Whether genetically-manipulated products would qualify as "hazardous substances" or "pollutants" was questioned.[150] The term "hazardous substance" is defined by reference to lists of harmful substances specified in six statutes including CERCLA.[151] However, no organisms or by-products have been included in any of the specified statutes,[152] and some have argued that, because CERCLA focuses "to a significant degree on toxic and disease-producing substances," most genetically-engineered organisms which would be deliberately released into the environment would not be covered by the statute because they are not likely to pose such a threat.[153]

C. *Other Environmental Statutes*

In addition to those statutes under the EPA's jurisdiction, two other

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RCRA [did] not grant EPA significant authority to regulate deliberate releases." *Id.*

148. McChesney & Adler, *supra* note 42, at 10,378.

149. Novick, *supra* note 3, at § 18.04[3].

150. *See* McChesney & Adler, *supra* note 42, at 10,379.

151. 42 U.S.C. § 9601(14) (1986). These include:

(a) substances designated under Section 311(b)(A) of the Clean Water Act, (b) any element, compound, mixture, solution, or substance designated pursuant to Section 102 of CERCLA, (c) any hazardous waste having the characteristics identified under or listed pursuant to Section 3001 of the Solid Waste Disposal Act (RCRA), (d) any toxic pollutant listed under Section 307(a) of the Federal Water Pollution Control Act, (e) any hazardous air pollutant listed under Section 112 of the Clean Air Act, (f) any imminently hazardous chemical substance or mixture for which EPA has taken action pursuant to Section 7 of the Toxic Substances Control Act, 42 U.S.C. 9601(14).

152. Korwek & de la Cruz, *supra* note 42, at 374.

153. McChesney & Adler, *supra* note 42, at 10,379. Under CERCLA the EPA is also authorized to respond to a release or threatened release of a "pollutant or contaminant" which poses an imminent and substantial danger to public health or welfare. The term "pollutant or contaminant" specifically includes "disease-causing agents." *See* 42 U.S.C. § 9604(a)(2) (1982). However, under CERCLA the EPA can only recover from liable parties for clean-up costs associated with the release of hazardous substances, not pollutants or contaminants. *See, e.g.*, McChesney & Adler, *supra* note 42, at 10,379. Private parties responsible for the release of pollutants or contaminants have no liability for the costs of response, or damages to natural resources. *See* Novick, *supra* note 3, at § 18.04[3].

A further disadvantage of CERCLA as a regulatory tool for biotechnology is that it provides only for cleaning up past pollution "while the critical problem at [the early] stage of environmental regulation of biotechnology has been accurately assessing the potential for harm from proposed releases and controlling the releases to avoid the harm." McChesney & Adler, *supra* note 42, at 10,379.

environmental statutes were discussed early on as relevant to the regulation of biotechnology—the National Environmental Policy Act (NEPA) and the Endangered Species Act (ESA). NEPA, passed by Congress in 1969 in response to reports of increasing harm to the environment, requires federal agencies to prepare an environmental impact statement (EIS) for all "major federal actions" which "significantly affect" the quality of the environment.[154] Major environmental actions include not only activities directly undertaken by federal agencies, such as the passage of new regulations or the construction of a federal highway or dam, but also private actions that require federal funding, permits, licenses, or other approval.

NEPA is primarily a procedural law, *i.e.*, it requires federal agencies to comply with specific procedures before undertaking certain actions. Actions that are unlikely to affect the environment are categorically excluded from the Act's requirements, as are actions that are subject to a similar review process under another statute.[155] Before undertaking an action which is not categorically excluded, a federal agency must prepare an environmental assessment (EA)—a brief document that sets forth the potential environmental impacts of a proposed federal action and possible alternatives to the action.[156] Based on the EA, the agency will determine whether the action will have a "significant environmental impact." If the agency finds that the action will not have such an impact, the agency must issue a formal "finding of no significant impact."[157] Alternatively, if the agency determines that the action will have a significant environmental impact, a full blown environmental impact statement must be prepared. The EIS is a very detailed report of the potential environmental impacts of a proposed action and alternatives to the action. The report is typically several hundred pages long, sometimes thousands of pages, and is both costly and time-consuming to prepare.[158]

Environmental and citizens groups have frequently used NEPA as a vehicle to delay or prevent federal actions or private actions requiring federal approval. They have accomplished this by bringing suits against federal

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154. 42 U.S.C. § 4332 (1982).

155. This latter exemption, referred to as the doctrine of "functional equivalence," has been successfully invoked only by the EPA. *See* J. GIBBS, *supra* note 77, at 138.

156. *See* 40 C.F.R. § 1508.9(b) (1988).

157. *See* 40 C.F.R. § 1508.13 (1988).

158. The statement must include a description of:

(i) the environmental impact of the proposed action;

(ii) any adverse environmental effects which cannot be avoided should the proposal be implemented;

(iii) alternatives to the proposed action;

(iv) the relationship between local short-term uses of man's environment and the maintenance and enhancement of long-term productivity; and

(v) any irreversible and irretrievable commitments of resources which would be involved in the proposed action should it be implemented.

42 U.S.C. § 4332(2)(C)(i-v) (1982).

agencies claiming, among other things, that: (1) NEPA was applicable when the agency determined that it was not, (2) the relevant agency did not prepare an EA or EIS when one was necessary or, (3) if an EA or EIS was prepared, that it was not adequate or the appropriate procedural steps were not followed in its preparation. NEPA was used for the first time as a tool to delay R-DNA experimentation in 1978. In *Mack v. Califano*[159] a child living near a federal cancer research institute brought suit against the Department of Health and Human Services asserting that a high risk R-DNA experiment proposed by the laboratory and permitted under the NIH *Guidelines* could have adverse environmental or public health consequences in the surrounding community if an organism were to escape from the laboratory. The plaintiff further alleged that the EIS prepared when the initial NIH *Guidelines* were promulgated did not adequately address the potential dangers of such an experiment. The federal district court, however, determined that the initial EIS was adequate and that the experiment could go forward.[160]

The Endangered Species Act (ESA)[161] was also listed as a mechanism for the regulation of the release of genetically altered organisms into the environment. ESA, which calls for the establishment of a program to protect endangered and threatened species and their habitats, is administered by the Fish and Wildlife Service (FWS) within the Department of the Interior. It is similar to NEPA in that it "imposes affirmative requirements only upon federal agencies, not private companies."[162] All federal agencies "must consult with the FWS before authorizing or funding 'any action' that may jeopardize any endangered species."[163] All endangered or threatened species are listed by the FWS in the Federal Register. If the FWS concludes that an agency action may harm an endangered species, the agency is expected to utilize various techniques to eliminate the harm.[164]

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159. Mack v. Califano, 447 F. Supp. 668 (D.D.C. 1978).

160. Subsequent cases brought under NEPA to delay biotechnology research are discussed *infra* notes 358, 365, 366, 375.

161. Endangered Species Act, 16 U.S.C. §§ 1531-43 (1982).

162. J. GIBBS, *supra* note 77, at 147.

163. *Id.*

164. Both EPA and USDA actions regarding deliberate releases may be subject to the ESA. The EPA has had a well-established procedure for consulting with FWS regarding the approval of new pesticides. According to one source, under FIFRA the EPA "assesses the potential risk to endangered species for roughly 700 new pesticide uses annually. Between 1980 and 1984, EPA requested approximately 40 consultations with FWS . . . . In two-thirds of these instances, FWS determined that an endangered species would be in jeopardy if the [action] were approved without modification." J. GIBBS, *supra* note 77, at 148. As of 1984 the EPA had no comparable program for FWS consultation under TSCA and the USDA had not developed a formalized review procedure under the ESA for deliberate releases which it may approve. Gibbs raises the possibility that ESA may not apply to TSCA as the consultation requirement of ESA is only triggered by "any action authorized, funded, or carried out" by an agency, and that TSCA does not require permits, only notification of the EPA. However, the authors point out that the EPA is now considering whether an ESA review should be estab-

Finally, although not a statute, Executive Order No. 11,987[165] was cited as a possible source of authority for the regulation of products developed through biotechnology. The order, signed by President Carter in 1977, provides in relevant part that executive agencies shall: (1) restrict the introduction of exotic species "into the natural ecosystems on lands and waters which they own, lease, or hold for purposes of administration; and shall encourage the States, local governments, and private citizens to prevent the introduction of exotic species into natural ecosystems of the United States" and (2) to the extent they have been authorized by statute, "restrict the introduction of exotic species into any natural ecosystem in the U.S." Exotic species are defined as "all species of plants and animals not naturally occurring, either presently or historically, in any ecosystem of the United States."

The order is of limited value in regulating deliberate releases of microorganisms, however, as the definition of exotic species is limited to plants and animals. Furthermore, the order is limited to species which do not occur naturally in any ecosystem of the United States. Thus, "if a plant or animal ever existed naturally, it would not be regulatable under the order even if it were no longer found in nature. Neither would the directive prevent the release of organisms into areas where they are not indigenous, since it applies only to those species not occurring naturally in any ecosystem of the United States."[166]

D. *Regulation of Genetically-Engineered Organisms by the FDA*

Prior to 1984 the FDA had not promulgated any regulations explicitly addressing genetically engineered products. Thus, the Agency regulated such products under its existing regulatory framework. The FDA's regulatory authority, in general, stems from the Food, Drug and Cosmetic Act (FDCA),[167] and sections of the Public Health Service Act.[168] These statutes give the FDA the authority to regulate foods, human and animal drugs, human biologics (such as vaccines), and medical devices (such as human enzymes used in *in vitro* diagnostic systems).[169]

The major issue underlying most of the early discussion of FDA regulation of biotechnology-derived products was whether these products should be regulated on a product or process basis, *i.e.*, whether they should be regu-

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lished for TSCA-regulated products. *Id.* at 150.

165. Executive Order No. 11,987, 3 C.F.R. § 116 (1977).

166. Korwek & de la Cruz, *supra* note 42, at 355. In addition, the utility of the order for regulating deliberate releases is further restricted because the order only applies to executive agencies. This is particularly limiting because the EPA, which is the agency most able to regulate environmental harms, is not within the executive branch. *See id.*

167. 21 U.S.C. §§ 301-92 (1982).

168. 42 U.S.C. §§ 262-63 (1982).

169. Karny, *Frankensteins*, *supra* note 42, at 842.

lated differently from similar products produced by conventional means.[170] The FDA was and is structured along product lines, with separate centers responsible "for all regulatory activities regarding specific classes of products" such as foods, drugs, biologics, and medical devices.[171] From the outset the FDA took the approach that products manufactured by the new biotechnologies would not be handled by a separate biotechnology unit but would be regulated on a case-by-case basis in accordance with their product class.[172]

1. *Regulation of Foods*

FDA authority to regulate food products developed by biotechnology is grounded in its authority to ensure that the product is not adulterated or misbranded and, in some cases, its authority to require pre-market clearance of the product. The latter is the agency's most effective regulatory mechanism. The regulatory system classifies food products into four groups: (1) food additives; (2) substances that are generally recognized as safe (GRAS);[173] (3) prior-sanctioned ingredients;[174] and (4) whole foods.

Only new food additives require pre-market clearance. Such food additives, however, are broadly defined to include any substance that is not GRAS or prior-sanctioned, 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."[175] Pre-market clearance requires extensive animal and human testing to ensure that the additive is safe for human consumption.

Food additives are regulated generically, *i.e.*, once a food additive is ap-

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170. *See, e.g.*, Note, *An Overview of FDA Regulation of Biotechnology Derived Products: Dealing with the Collision of Science and Society*, 11 RUTGERS COMPUTER & TECH. L.J. 501, 510 (1985) [hereinafter Note, *An Overview of FDA Regulation*]; Korwek & Trinker, *Perspectives on the FDA Status of Drug Products Manufactured by the Recombinant DNA Technique*, 36 FOOD DRUG COSM. L.J. 517, 518 (1981) [hereinafter Korwek & Trinker]; Comment, *Regulation of Genetically Engineered Foods Under the Federal Food, Drug, and Cosmetic Act*, 33 AM. U.L. REV. 899, 913 (1984) [hereinafter Comment, *Regulation of Genetically Engineered Foods*].

171. McGarity & Bayer, *supra* note 42, at 504.

172. Zoon, *The Impact of New Biotechnology on the Regulation of Drugs and Biologics*, 41 FOOD DRUG COSM. L.J. 429, 430 (1986). The FDA, however, has established its own Recombinant-DNA Coordinating Committee, which provides an agency-wide vehicle for information exchange and discussion of policies regarding genetically engineered products.

173. A GRAS substance is defined as a substance that is "generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use." 21 U.S.C. § 321(s) (1982).

174. Prior sanctioned substances are those that received official approval by the FDA prior to the passage in 1958 of the Food Additive Amendment to the FDCA. 21 C.F.R. §§ 181.1, 181.5 (1988).

175. 21 U.S.C. § 321 (1982).

proved, the agency promulgates a food additive regulation that specifies the chemical structure (identity) and purity limitations on use of the additive. Any manufacturer can market the additive if its product meets the specified regulatory conditions.[176] At least one author argued that, because the food additive regulations only contain criteria for chemical structure, purity, and use, and do not include process standards, the manufacture via biotechnology of food additives for which there are existing regulations should not require pre-market clearance unless the technology changes the chemical identity or creates impurities that adulterate the product.[177]

Whether a substance that was GRAS would remain so if manufactured by biotechnology was also an open issue. To establish GRAS status for food additives used after 1958, the regulations provide that "safety must be proven through scientific procedures, *i.e.*, scientific evidence of safety published in the literature or otherwise widely disseminated so as to become common knowledge among scientists knowledgeable about the safety of food ingredients."[178] The FDA had issued a list of substances which met the GRAS requirements, either for all uses or for specific uses. The regulations which listed substances as GRAS "usually include[d] general statements about [their] method of manufacture."[179] In a 1982 article on the topic, Korwek concluded that many ingredients that were listed as GRAS but which were subsequently manufactured by biotechnology "would not meet the requirements of the regulation because conventional methods of manufacture were specified . . . ."[180] Furthermore, Korwek predicted that, although the FDA "had acknowledged that a change in manufacturing process [did] not necessarily alter the GRAS status of an ingredient," the FDA would probably still "view use of biotechnology as presumptively affecting GRAS status because it is not a generally recognized method of production."[181]

2. *Adulteration and Misbranding*

In addition to its pre-market clearance authority, the FDA may regulate foods and food additives under FDCA adulteration and misbranding provisions. A food may be considered adulterated under FDCA for several rea-

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176. *See* Korwek, *FDA Regulation of Biotechnology as a New Method of Manufacture*, 37 FOOD DRUG COSM. L.J. 289, 293 (1982) [hereinafter Korwek, *FDA Regulation of Biotechnology*] (detailed description of the regulation of food additives).

177. *Id.* This conclusion is based on the assumption that the additives are used in accordance with good manufacturing practices.

178. *Id.* at 295 (citing 21 C.F.R. §§ 170.3(h), 170.30(b) (1981)).

179. *Id.* at 296.

180. *Id.*

181. *Id.* at 297. In contrast, Korwek pointed out that substances that were previously sanctioned would remain so even if manufactured by use of biotechnology because the approval went to the substance, "not to its method of manufacture." *Id.* at 296.

sons. Where foods contain an "added substance," the primary basis for a finding of adulteration is that the food "bears or contains [a] poisonous or deleterious substance which *may render* it injurious to health."[182] If the food does not contain an added substance, however, it will not be considered adulterated "if the quantity of such substance in such food does not *ordinarily render* it injurious to health."[183] What constitutes an "added substance" has been liberally defined by the courts to include anything incorporated into a food "as the result of any human intervention."[184] The second principal basis for a finding of adulteration is that the food "bears or contains any added poisonous or added deleterious substance . . . which is unsafe within the meaning of [the statute]."[185] In this case the FDA has defined an added substance as one which "is not an inherent constituent of the food" *or* which is present in a food as a result of "human intervention."[186] Under either definition it appears that a genetically altered food additive would be considered an added substance; a food produced by biotechnology, which included additional genetic material or genetically modified organisms, would be considered to contain an added substance.[187] As a result, the FDA would only have to show that the substance met the less stringent "may render" standard before taking enforcement action.

At least one author has argued that the FDA should not use the "may render" standard in determining whether a genetically engineered food is adulterated because that standard is not applied to foods developed by hybridization.[188] Under this view genetically engineered foods and food additives should not be regulated any differently from foods produced by hybridization if scientists are able to achieve the same product by both methods. However, foods treated with genetically modified microbes or additional genetic material that might acquire toxicants from external sources should be regulated under the "may render standard for foods containing added toxicants rather than as foods containing endogenous toxicants under the ordinarily render standard."[189]

Under the adulteration provisions of FDCA, the FDA has issued good manufacturing practice (GMP) regulations for both foods and drugs. The food regulations set forth guidelines for food manufacturers, "including per-

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182. 21 U.S.C. § 342(a)(1) (1982) (emphasis added).

183. *Id.*

184. Gibbs & Kahan, *Federal Regulation of Food and Food Additive Biotechnology*, 38 ADMIN. L. REV. 1, 12 (1986) [hereinafter Gibbs & Kahan].

185. 21 U.S.C. § 342(a)(2)(A) (1982).

186. *See* Gibbs & Kahan, *supra* note 184, at 12.

187. *But see* Jones, *Food Safety Aspects of Gene Transfer in Plants and Animals: Pigs, Potatoes and Pharmaceuticals*, 43 FOOD DRUG COSM. L.J. 351 (1988) (the author subsequently raised a variety of ways of characterizing transplanted genes, some of which could lead to a determination that the genes were not added) [hereinafter Jones, *Food Safety*].

188. Comment, *Regulation of Genetically Engineered Foods*, *supra* note 170, at 916.

189. *Id.*

sonnel qualifications, process controls, the condition of facilities, and general principles for maintaining sanitation."[190] These regulations provide additional authority for the FDA to assess the development of a product as well as the product itself.

3. *Regulation of Drugs*

As was the case in the area of new foods, the controversial issue with respect to the regulation of newly created drugs and devices was whether biotechnology-derived products, that have been previously approved when manufactured by conventional techniques, should be subject to extensive new testing requirements, or whether the final products are so similar in nature to conventionally-developed products that little, if any, new testing should be required.

The FDA has two methods of ensuring that drugs are safe for human application: (1) all drugs must meet the adulteration and misbranding provisions of FDCA; and (2) all *new* drugs must be pre-cleared prior to marketing. Pre-clearance requires that new drugs[191] may not be marketed unless they have been approved as safe and effective on the basis of adequate and well-controlled clinical investigations. To conduct clinical trials on humans, a new drug developer must file a notice of claimed investigational exemption for a new drug (IND) containing results of acute, subacute, and chronic toxicity testing on animals to ensure safety.[192] Once the animal and human testing is complete, the developer must file a new drug application (NDA) with the FDA for approval. An NDA contains the results of all the clinical and non-clinical tests performed on the drug, a full list of articles used as components of the drug, a full statement of the drug's composition, a full description of the methods used in manufacturing, samples of the drug components, and specimens of the proposed labeling.[193] This complete NDA procedure typically requires "many years of testing and large monetary expenditures."[194]

In certain cases a complete NDA is not required before a new drug is

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190. Gibbs & Kahan, *supra* note 184, at 23. In addition, the FDA could have some control over the manufacture of genetically engineered food additives by requiring the manufacturer to prepare an environmental assessment or environmental impact statement prior to approval of the additive. FDA decisions are subject to NEPA and the FDA has stated "that an environmental assessment [would] be required for all food additive petitions, even if the food additive is naturally occurring." *Id.* at 21-22. If the agency determined that the manufacturing process could have a significant effect on the environment, it could require the manufacturer to prepare a detailed environmental impact statement. *Id.* at 21.

191. A new drug is any drug that is not generally recognized as safe and effective (GRASE) for its intended use. 21 U.S.C. § 321(p) (1982).

192. 21 U.S.C. § 355(i) (1982); 21 C.F.R. §§ 50, 56, 312.1 (1988). *See also* Korwek & Trinker, *supra* note 170, at 521.

193. Korwek & Trinker, *supra* note 170, at 521.

194. *Id.*

marketed.[195] For example, an abbreviated NDA (ANDA) may be filed for generic drugs which are copies of pioneer drugs which have already been marketed. The ANDA requires the submission of bioavailability data and evidence of compliance with FDA good manufacturing practices (GMP) regulations.[196]

If the NDA holder wishes to market an approved drug under conditions other than those approved in the NDA, it must submit a supplemental new drug application (SNDA) for FDA approval.[197] The SNDA provides the most recent reports, superseding those submitted as part of the original application.[198]

These abbreviated review procedures only apply to new drugs. Drugs that do not meet the definition of "new drugs"—*i.e.*, drugs that are generally recognized as safe and effective (GRASE)—are statutorily exempted from pre-market clearance.[199] However, such drugs are still subject to the adulteration and misbranding provisions of the Act. Thus, drugs cannot contain harmful impurities as a result of the method of manufacture or otherwise, and drug manufacturers must comply with good manufacturing practices and the relevant labeling requirements.

The regulatory scheme raised the question whether a drug that had previously been approved as a new drug when produced by conventional means would also be approved if produced by biotechnology; the alternative would be an abbreviated or a complete NDA. The FDA stated explicitly in 1983 that it would require new applications for all products obtained via R-DNA technology:

> The amount of data required [would] vary, [however], depending on: (1) the proposed use of the product; (2) whether the product [was] identical to a previously approved product; (3) how long an administration of the product to patients [was] planned; (4) the previous clinical experience with the conventionally produced product; and (5) the applicant's clinical experience with rDNA-derived substances. The new applications [would] be required even if the product [was] identical in molecular structure to a naturally occurring substance or a previously approved product produced in a conventional way.[200]

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195. Note, *An Overview of FDA Regulation*, *supra* note 170, at 516.

196. *Id.*

197. 21 C.F.R. § 314.70(a) (1988).

198. *See* Korwek & Trinker, *supra* note 170, at 522.

199. Korwek & Trinker, *supra* note 170, at 524.

200. Note, *An Overview of FDA Regulation*, *supra* note 170, at 522. *See also* OFFICE OF BIOLOGIC RESEARCH AND REVIEW, CENTER FOR DRUGS AND BIOLOGICS, FDA, POINTS TO CONSIDER IN THE PRODUCTION AND TESTING OF NEW DRUGS AND BIOLOGICALS PRODUCED BY RECOMBINANT DNA TECHNOLOGY (Apr. 10, 1985). Prior to 1983 the FDA had argued that "new drug" referred to the entire drug product, not just its active ingredients. Korwek, *FDA Regulation of Biotechnology*, *supra* note 176, at 300. Thus, a new drug with an active ingredient identical to an already approved drug would still require an NDA. *Id.* The Supreme Court affirmed the Agency's position in *United States v. Generix Drug Corp.*, 460 U.S. 453 (1983). The practical

The basis of the FDA's cautious approach to R-DNA manufactured drugs is similar to its cautious approach to other new drugs and includes the following:

1) The molecular structure of some [R-DNA-derived] products is different from that of the active molecules in nature.

2) Despite some experience with drugs derived from microorganisms there is meager, if any, experience with such substances employed as drugs in humans with continued administration over many months or years.

3) [The FDA] will need to ensure that the quality assurance within the manufacturing process is adequate to detect the occurrences of mutations in the coding sequence of the cloned gene during fermentation.[201]

4) The constellation of contaminants is often different when a new technique is used.[202]

The FDA's approach, i.e., to "a priori classify all [R-DNA-derived] products as the type of new drugs that require full pre-clinical and clinical testing"—was considered inappropriate by some authors.[203] It was also burdensome on drug manufacturers since it "often requires a large amount of time, effort and funds, and usually results in a significant delay in reaching the marketplace."[204]

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effect of this interpretation was to subject all drugs to pre-market clearances. Korwek, *FDA Regulation of Biotechnology*, *supra* note 176, at 301. The FDA took the same approach to the question of whether a drug manufactured by new techniques could be considered GRASE: the entire newly manufactured drug (its inactive ingredients, method of manufacture, and finished dosage form) must be identical to the GRASE product.

201. Note, *An Overview of FDA Regulation*, *supra* note 170, at 524. *See also* Zoon, *supra* note 172, at 431.

202. Telephone interview with Dr. Henry Miller, Special Assistant to the FDA Commissioner for Biotechnology, in Rockville, Md. (Aug. 1988).

203. Korwek & Trinker, *supra* note 170, at 534.

204. Note, *An Overview of FDA Regulation*, *supra* note 170, at 524. Korwek and Trinker argued that R-DNA-derived drugs should be divided into three groups for purposes of regulation. First, they asserted, where the R-DNA-derived active ingredient was chemically identical to its traditionally manufactured counterpart, an ANDA or SNDA "should be permitted, as if the product were manufactured by more conventional techniques." In support of this position, they argued that "[s]ince abbreviated review is typically available for such products made by more traditional methodology, there [was] no legal or scientific justification for automatically requiring full clinical testing when the R-DNA technique [was] used to prepare an identical ingredient." Second, they identified drugs where the R-DNA-derived active ingredient appeared to have only insignificant chemical deviations from the drug entity manufactured by conventional means. For this group, the authors also argued that an ANDA, SNDA, or NDA with less than full clinicals should be permitted. A biological assay test could be used to determine if any changes would affect the safety or therapeutic equivalence of the drug. The third group were those drugs where biotechnology significantly altered the chemical identity of the active ingredient. For this group the authors agreed that full clinical testing was justified. Korwek & Trinker, *supra* note 170, at 532.

4. *Biologics and Medical Devices*

The FDA also has the authority to regulate biologics and medical devices for human use—two areas where biotechnology is making significant inroads. Biologics include "viruses, vaccines, serums, toxins, antitoxins, allergenic products, blood and blood components."[205] Although this description appears straightforward, biotechnology has created some confusion over whether certain products are biologics or drugs. The FDA has created a committee to determine which center—the Center for Medical Devices or the Center for Drugs—will review products not clearly fitting into one category or another.[206]

Biologics are regulated somewhat differently from other products under the jurisdiction of the FDA.[207] Unapproved biological products are treated as new drugs during the investigational new drug application phase, but then are issued a license specifying the conditions of manufacture. Both the manufacturing facilities and the product must meet standards "designed to ensure safety, purity and potency."[208] Biologics regulation includes no provision for abbreviated approval processes; thus all biologics whether or not made by R-DNA technology require a complete product license application.[209]

Medical devices, in contrast to biologics, are health care products which do not achieve any of their "principal intended purposes through chemical action within or on the body of man or other animals" and which are not "dependent upon being metabolized for the achievement of any of [their] principal intended purposes."[210] Medical devices include a variety of diagnostic aids such as "reagents (chemicals), antibiotic sensitivity discs (for determining which antibiotic to use for a particular patient) and test kits for *in vitro* (outside the body) diagnosis of disease (*e.g.*, diabetes, AIDS) and other conditions (*e.g.*, pregnancy)."[211]

The extent of FDA authority to regulate new methods of manufacturing of medical devices is based on the class of the device. The FDCA established three categories of medical devices, each with separate regulatory require-

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205. *See* 42 U.S.C. § 262(a) (1982).

206. *See* KORWEK, 1988 BIOTECHNOLOGY REGULATIONS, *supra* note 129, at 43. The difference between a biologic and a medical device may also be an area of some confusion. While the FDA has stated that "any monoclonal antibody product prepared by hybridoma technology that is intended for *in vivo* use or for *in vitro* testing of a licensed biological product is a biological product subject to licensure under the PHS Act," the vast majority of monoclonal products are regulated as medical devices. *Id.* (citing 48 Fed. Reg. 50,795 (1983)).

207. Biological products for human use are regulated primarily under the Public Health Service Act. 42 U.S.C. § 262 (1982).

208. Note, *An Overview of FDA Regulation*, *supra* note 170, at 511. *See also* 42 U.S.C. § 262(d) (1982); 21 U.S.C. §§ 351-52 (1982).

209. Note, *An Overview of FDA Regulation*, *supra* note 170, at 511.

210. 21 U.S.C. § 321(h) (1976).

211. Note, *An Overview of FDA Regulation*, *supra* note 170, at 511.

ments—those in Class I requiring relatively less regulation than those in Class III.

> Manufacturers of Class I and Class II devices must file a premarket notification [a 510(k) notification] with the FDA at least 90 days prior to commercial distribution. Premarket approval demonstrating that the device is safe and effective is not required as long as the new product is "substantially equivalent" in safety and effectiveness to [a previously approved device].[212]

In contrast, a Class III device must be approved on a product-by-product basis, even if the device is identical to a previously approved device. The manufacturer "must file a premarket approval application (PMAA) containing laboratory or clinical data to establish that the device is safe and effective."[213]

Use of biotechnology to prepare Class I or Class II medical devices does not automatically change their classification to Class III. The method of manufacture is only relevant to class insofar as it alters the safety and effectiveness of the product.[214] Thus, manufacturers of new Class I or Class II devices made by biotechnology "must demonstrate that such devices are substantially similar to products made by conventional techniques in order to avoid conducting the safety and efficacy studies typically required in premarket approval applications for Class III devices."[215] Also, manufacturers of devices in any of the three classes who previously prepared a device by conventional methods but who now use biotechnology must submit a 510(k) notification to the FDA.

> In this respect, the 510(k) submission is much like a supplemental application filed for a change in manufacturing process of an approved drug. If the FDA believes that use of biotechnology poses safety or efficacy problems, it [can] then delay marketing until adequate data are developed to prove otherwise, or [it can] reclassify the product as a new, Class III device that requires agency approval and extensive premarket testing.[216]

Some have argued that the approach taken by the Center for Medical Devices is a more reasoned one than that taken by the Center for Drugs, under

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212. *Id.* In addition, "[m]anufacturers of a Class I device must satisfy the general provisions of the Act relating to misbranding, adulteration, and compliance with . . . GMPs. Class II devices [must also] conform to performance standards, which can include specification as to construction, components, ingredients, and properties of the device, as well as to clinical testing and other studies relevant to technical characteristics." Korwek, *FDA Regulation of Biotechnology*, *supra* note 176, at 303.

213. Note, *An Overview of FDA Regulation*, *supra* note 170, at 511.

214. *Id.*

215. Korwek, *FDA Regulation of Biotechnology*, *supra* note 176, at 304.

216. *Id.* at 304-05. Korwek also points out that 510(k) submissions have been successfully used to market previously approved Class III devices.

which a complete NDA is required for all new drugs manufactured by biotechnology.

5. *Public Health Service Act*

The other potential legal authority for FDA regulation of biotechnology-derived products is section 361 of the Public Health Service Act (PHSA),[217] which gives the agency authority "to promulgate regulations in cooperation with the Center for Disease Control 'to prevent the introduction, transmission, or spread of communicable diseases.' "[218] Although this broad authority appears to provide a sufficient basis to control all biotechnology activities, the statutory language limits the application of the Act to the protection of human health.[219] PHSA defines communicable disease as "illness due to an infectious agent . . . which is transmitted directly or indirectly *to a well person* from an affected person, animal or arthropod . . . ." Thus, as one author pointed out, a supportable finding of a connection between biotechnology products and human disease would be necessary to justify regulation of biotechnology activity under the Act.[220] Since most consider such a finding unlikely, the PHSA has not been relied upon by the FDA to regulate products developed by biotechnology.

E. *Regulation by the USDA*

Prior to 1984 the USDA had had significant involvement with biotechnology by virtue of the fact that it conducted and funded biotechnology research as applied to plants and animals, and also regulated the use of animal biologics, plants, plant pests, non-human animal pests, and animals used for food. In 1979 the USDA endorsed and adopted the NIH *Guidelines*, requiring compliance with the *Guidelines* in all research conducted by USDA departments and grantees.[221] Soon thereafter, the USDA established the Agriculture Recombinant DNA Research Committee (ARRC) to support the NIH RAC and to oversee and coordinate biotechnology matters among the

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217. 42 U.S.C. § 264 (1982). *See also* 21 C.F.R. § 5.10 (1988) (transferring authority under the Public Health Services Act from the Assistant Secretary for Health, DHHS, to the Commissioner of the FDA).

218. McGarity & Bayer, *supra* note 42, at 505 (quoting 42 U.S.C. § 264a (1982)).

219. Karny, *Frankensteins*, *supra* note 42, at 852. The statute specifically states that "[f]or purposes of carrying out and enforcing such regulations, the [regulatory authority] may provide for such inspection, fumigation, disinfection, sanitation, pest extermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings . . . ." 42 U.S.C. § 264 (1982).

220. Karny, *Frankensteins*, *supra* note 42, at 852.

221. *See* Statement of Policy for Regulations, Biotechnology Processes and Products, 49 Fed. Reg. 50,897-98 (1984) (citing Memorandum to Heads of Department Agencies: Guidelines for Research Involving Recombinant DNA Molecules (Oct. 15, 1979)).

various agencies in the USDA and the NIH.[222]

1. *Regulation of Plant and Animal Pests*

With respect to the regulation of plant and animal pests, the USDA has a significant number of statutes at its disposal for regulating biotechnology-derived products. The statutes include the Federal Plant Pest Act (FPPA)[223] and its precursor, the Plant Quarantine Act (PQA),[224] the Federal Noxious Weed Act (FNWA),[225] the Virus-Serum-Toxin Act (VSTA),[226] and the Act of February 2, 1903.[227] Several of the statutes, however, have a number of limitations which reduce their effectiveness in this regard.

For example, FPPA prohibits individuals from importing or transporting in interstate commerce any "plant pest" without a USDA permit. A plant pest is broadly defined to include a variety of organisms and parts of organisms which "can directly or indirectly injure or cause disease or damage in or to any plant or parts thereof."[228] The definition includes "insects and other nonvertebrate animals as well as microorganisms and parasitic plants . . . ."[229] Organisms that meet the definition are designated as plant pests and are listed in the Federal Register. Although the definition appears to cover a broad variety of organisms, a narrow reading of the statutory language would exclude organisms for which there is not a reasonable certainty that the organisms would be harmful to plants—a showing of a risk of harm would not be enough.[230]

A second limitation of the FPPA is that it applies only to the sale, transportation, and release of organisms, *not* to their production.[231] Nor does FPPA apply to intrastate movement; it covers only interstate transportation. Thus, the USDA would have difficulty reaching engineered organisms

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222. *Id.*

223. Federal Plant Pest Act, 7 U.S.C. §§ 150aa-150jj (1982).

224. Plant Quarantine Act, 7 U.S.C. §§ 151-64, 166-67 (1982).

225. Federal Noxious Weed Act, 7 U.S.C. §§ 2801-13 (1982).

226. Virus Serum Toxin Act, 21 U.S.C. §§ 151-58 (1982).

227. Act of Feb. 2, 1903, 21 U.S.C. § 111 (1982). Responsibility for implementing and administering these statutes rests with the Animal and Plant Health Inspection Service within the Department. *See id.*

228. *Coordinated Framework for Regulation of Biotechnology*, 51 Fed. Reg. 23,354 (1986).

229. McChesney & Adler, *supra* note 42, at 10,376. The FPPA actually expanded the much older Plant Quarantine Act, which prohibited the importation of organisms defined as nursery stock into the United States unless a permit was obtained from the USDA. Novick, *supra* note 3, at § 18.03[3][c]. The PQA authorized the USDA to institute a quarantine against plants of "any character whatsoever that [were] 'capable of carrying any dangerous plant disease or insect infestation.' " Gibbs & Kahan, *supra* note 184, at 29-30 (quoting 7 U.S.C. § 161 (1985)). *See also* Korwek & de la Cruz, *supra* note 42, at 357 (discussing the PQA as a means of regulating deliberate releases).

230. *See* Novick, *supra* note 3, at 18-29; McChesney & Adler, *supra* note 42, at 10,376.

231. McChesney & Adler, *supra* note 42, at 10,376.

that were produced and kept within the boundaries of a single state.[232]

The Federal Noxious Weed Act, another potential source for authority to regulate some biotechnology-derived products, was enacted in 1974 to control noxious weeds that might have "adverse effects upon man or his environment."[233] FNWA is in many ways similar to FPPA. For example, "noxious weeds" cannot lawfully be moved in interstate commerce or released under FNWA without a USDA permit.

Although the term "noxious weed" is defined in a manner that could provide the USDA with broad regulatory authority over genetically engineered plants,[234] the statute has significant limitations as a vehicle for the regulation of genetically engineered plants or plant pests. For example, FNWA does not prohibit the interstate movement of a noxious weed until the weed is specifically listed as a noxious weed by the USDA after notice and opportunity for public comment,[235] and plants "can only be regulated as noxious weeds if they cause serious injury"—anything less is insufficient.[236] Furthermore, the statute empowers the USDA to regulate only those weeds introduced from abroad, not those that originated within the United States.[237]

A third alternative available to the USDA in the regulation of plant and animal pests is the Act of February 2, 1903. The Act allows the USDA to promulgate regulations "to prevent the introduction of contagious, infectious, or communicable disease of animals and/or live poultry from a foreign country into any state of the United States or the District of Columbia, or from one state to another."[238] Under the statute's regulations, individuals who wish to make interstate shipments of such organisms, or import them, must submit to the USDA a permit application which describes the organisms, their use, and the safeguards to be observed in their handling.[239]

With respect to genetic engineering, according to one authority, "the statute provides USDA authority to prevent the introduction or halt the spread of genetically engineered organisms that manifest themselves as in-

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232. Novick, *supra* note 3, at § 18.03[3][c]. In addition to these shortcomings, the Act excludes from its jurisdiction organisms considered beneficial to plants "such as lady bugs, despite the potential for ecological disruption from such organisms." *Id.*

233. Noxious Weeds Act, 7 U.S.C. § 2801 (1982).

234. Noxious weed means "any living stage . . . of any parasitic or other plant of a kind . . . which is of foreign origin, is new to or not widely prevalent in the United States, and can directly or indirectly injure crops, other useful plants, livestock, or poultry or other interests of agriculture . . . or the public health." 7 U.S.C. § 2801 (1982).

235. Korwek & de la Cruz, *supra* note 42, at 349.

236. *Id.* at 350.

237. *Id.* In addition, Korwek and de la Cruz asserted that the statute limited USDA jurisdiction to plants that were "not new or not widely prevalent in the U.S." *Id.* They further argued that if a genetically engineered microbe also occurred in nature it would not necessarily be new and thus not subject to the Act. *Id.*

238. Novick, *supra* note 3, at 18-28 (quoting 21 U.S.C. § 111 (1982)).

239. *Id.*

fectious agents of animal disease."[240] Environmentalists have argued, however, that the statute would not "provide pre-release review or testing of organisms to determine if they are, or could be, infectious."[241]

2. *Regulation of Animal Biologics*

While the FDA has regulatory authority over human biologics, the USDA has the authority to regulate animal biologics. Under the Virus-Serum-Toxin Act (VSTA), the Secretary of Agriculture may "issue, suspend, and revoke licenses for the maintenance of establishments for the preparation of viruses, serums, toxins, and *analogous products* used in the treatment of domestic animals."[242] In addition, VSTA authorizes the secretary to "promulgate regulations that [might] be necessary to prevent the preparation, shipment, and sale of worthless, contaminated, dangerous, or harmful viruses, serums, toxins, antitoxins, or analogous products used in the treatment of domestic animals."[243] Under the Act the USDA has required the licensing of animal biologics and has prohibited the importation or interstate shipment of veterinary biologics that are "worthless, contaminated, dangerous, or harmful."[244] Prior to 1984 VSTA was limited in its effectiveness, however, in that it did not apply to products shipped intrastate or to products that were exported.

3. *Use of Genetically-Altered Organisms in Animals Used for Food*

The USDA is also responsible for the inspection of animals used for human food. Once genetic material is successfully transferred into a host animal and becomes part of that animal, the animal may be subject to the Federal Meat Inspection Act (FMIA)[245] or the Poultry Products Inspection Act (PPIA).[246]

FMIA requires the USDA to inspect specified food animals prior to slaughter and after slaughter. The purpose of the pre-slaughter inspection "is to remove from human food channels animals that are obviously unfit for human food because of discernible diseases, abnormalities, chemical poisoning, and central nervous system disorders."[247] The post-mortem inspection is

240. *Id.*

241. *Id.* In contradiction, Korwek points out that § 111 of the Act is very comprehensive and that the USDA could use it to require pre-release review. Telephone interview with Edward Korwek in Washington, D.C. (Sept. 1988).

242. Jones, *Genetic Engineering in Domestic Food Animals: Legal and Regulatory Considerations*, 38 FOOD DRUG COSM. L.J. 273, 277 (1983) (emphasis added) [hereinafter Jones, *Genetic Engineering*].

243. *Id.*

244. *Id.*

245. Federal Meat Inspection Act, 21 U.S.C. §§ 601-95 (1982).

246. Poultry Products Inspection Act, 21 U.S.C. §§ 451-70 (1982).

247. Jones, *Genetic Engineering*, *supra* note 242, at 274.

performed in order to remove from the human food channels meat that is "unfit for human food because of adulteration due to diseases or abnormalities discernible upon examination of internal organs and tissues."[248] FMIA requires the inspection of only a limited number of species—cattle, sheep, swine, goats, horses, mules, and other equines. Other species, such as game animals, are not inspected under the mandatory program (although they may be inspected for a fee).[249] Like FMIA, PPIA provides for pre- and postmortem inspection of poultry products. PPIA, however, has a much broader definition of species subject to inspection than does FMIA.[250]

The regulations implementing FMIA and PPIA provide that "no livestock used in any research investigation involving an experimental biological product, drug, or chemical shall be eligible for slaughter" unless certain specific conditions are met.[251]

Given the current regulatory scheme for inspection, the use of genetically altered organisms or genes in food animals could generate some problems for the USDA. For example, "some genetically engineered animals, such as chimerae and some hybrids, may differ substantially from animals that are currently inspected under the FMIA and PPIA."[252] USDA policy has been to inspect animals if they physically resemble species listed under FMIA or PPIA.[253] This policy may discourage genetic engineers who want tax-supported government inspections from developing new varieties of hybrid livestock "that differ in appearance from cattle, sheep, swine, goats, horses, mules, and other equines."[254] Furthermore, as Jones points out:

> The proliferation of genetically engineered food animals will place much greater strain on our current system of food safety, inspection, standards, and labeling than the breeding of [unique hybrids] did . . . . The social response to that strain will most certainly require new and innovative public policy making, rulemaking, and perhaps new legislation as well.[255]

Thus, prior to 1984 the power of the USDA to regulate biotechnology-derived organisms and plants for deliberate release or biotechnology-altered animals for human food under its statutory and regulatory schemes was

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248. *Id.*

249. *Id.* at 274-75.

250. *Id.* at 275. Under FPIA "poultry" means any domesticated bird. 21 U.S.C. § 453(e) (1982).

251. Jones, *Genetic Engineering*, *supra* note 242, at 281.

252. Gibbs & Kahan, *supra* note 184, at 31 (quoting 49 Fed. Reg. 50,856, 50,903 (1984)).

253. *See* Jones, *Genetic Engineering*, *supra* note 242, at 279.

254. *Id.*

255. *Id.* at 287. Another problematic area in the use of gene transfer in domestic food animals is whether the transferred genes will be considered food additives, animal drugs, or animal biologics. If the process is considered to result in a drug or food additive, it will be regulated by the FDA. If it is considered to result in a biologic, it will be regulated by the USDA. *See* Jones, *Genetic Engineering*, *supra* note 242, for a more detailed discussion of this dilemma.

open to considerable debate.

F. *OSHA*

Prior to 1984 the Occupational Safety and Health Act (OSHA)[256] was also cited as a potential source of statutory authority for regulating biotechnology in the area of worker safety. OSHA is aimed at protecting employees from workplace hazards and thus may be useful in controlling risks associated with the manufacture of biotechnologically-produced organisms. Some have argued, however, that OSHA has little power to regulate such applications because "its regulatory authority is generally dependent upon a showing of actual, palpable risk to worker health or safety."[257] Under OSHA three mechanisms are available to regulate workplace standards: (1) the general duty clause; (2) authority under section 6(b); and (3) emergency standards. Yet none of these provisions may provide the agency with the authority to regulate industrial applications of biotechnology.

Under the general duty clause, the agency is limited to regulating "recognized" hazards that are likely to cause death or serious bodily injury.[258] According to Korwek:

> Although it is arguable that a few applications of R-DNA techniques involving pathogenic agents pose "recognized" hazards and that some applications are likely to "cause death or serious bodily injury" as well, it is doubtful whether most current industrial applications of the new technology meet either of these two elements, both of which are necessary to establish a duty clause violation.[259]

Furthermore, even if biotechnology posed a hazard likely to cause serious harm, OSHA could not regulate the hazard unless there were "generally known and acceptable" tests to detect such a hazard.[260] No such tests exist.

Section 6(b)(5) of OSHA provides that the agency may promulgate standards applicable to toxic materials or harmful physical agents. Although theoretically this provision could provide the agency with the authority necessary to regulate hazards associated with the biotechnology industry, two Supreme Court cases have limited the agency's rulemaking ability under this section to cases where the agency has substantial evidence of a significant risk posed by the industrial practice.[261]

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256. Occupational Safety and Health Act, 29 U.S.C. §§ 651-78 (1982).

257. Korwek, *OSHA Regulation of Industrial Applications of Recombinant DNA Technology*, 50 CINCINNATI L. REV. 284, 286 (1981) [hereinafter Korwek, *OSHA Regulation*].

258. *Id.* at 296.

259. *Id.* at 297-98. This statement is based on the assumption that virtually all of the techniques used to manufacture R-DNA products use well-characterized systems such as *E. coli*.

260. *Id.* at 298.

261. *See* Industrial Union Dept., AFL-CIO v. American Petroleum Inst., 448 U.S. 607 (1980); American Textile Mfrs. Inst., Inc. v. Donovan, 452 U.S. 490 (1981).

Finally, the authority available to the agency to promulgate emergency standards is limited to cases where employees are exposed to "grave danger."[262] To meet this requirement, the agency must show "a risk of incurable, permanent or fatal consequences to workers, curable or temporary effects on health are not sufficient evidence that grave danger exists."[263] Thus, OSHA (like several of the other sources cited) had limitations which made its application to biotechnology questionable.

V. Regulation from 1984 to 1986

In the early 1980s Congress became concerned about the fragmented and piecemeal nature of the federal regulatory structure for commercialization of biotechnology.[264] Specifically, the regulatory scheme was criticized by Senator Albert Gore as a "balkanized" regime of oversight.[265] Gore further cited the limited expertise of the agencies involved as grounds for a new approach to the problem.[266] Biotechnology companies were also concerned about the regulatory maze and jurisdictional disputes among agencies and were reportedly hesitant to invest in new product development.[267]

In response to these concerns, in April 1984 the administration, under the auspices of the White House Cabinet Council on Natural Resources and the Environment (now the Domestic Policy Council), established a working group on biotechnology, which operated through the Office of Science and Technology Policy (OSTP). The task of the working group was to "determine whether the existing regulatory apparatus was adequate to consider the safety and health and environmental effects of modern biotechnology as its products and processes move[d] from contained research laboratories to the marketplace."[268] In December 1984 the working group published its results and concluded: "At the present time, existing statutes seem adequate to deal with the emerging processes and products of modern biotechnology."[269] The group went on to say, however, that "[t]he current scientific review apparatus is . . . not designed to respond to all the scientific issues surrounding commercialization of biotechnology including the health and broad environmental effects of new commercial processes and products."[270] The working group proposed a new framework for the regulation of biotech-

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262. Korwek, *OSHA Regulation*, *supra* note 257, at 311.

263. *Id.* at 312.

264. Gore & Owens, *supra* note 15, at 343. These concerns were set forth in a report prepared by the Subcommittee on Investigations and Oversight of the House Committee on Science and Technology in June 1983.

265. *Id.*

266. *Id.*

267. Note, *Rutabaga*, *supra* note 15, at 1541.

268. *Id.*

269. *Proposal for a Coordinated Framework for Regulation of Biotechnology*, 49 Fed. Reg. 50,858 (1984).

270. *Id.* at 50,904.

nology. The proposal included a "scientific advisory mechanism for the assessment of important issues and interagency coordination."[271] The mechanism consisted of a two-tiered structure composed of a biotechnology science board at the first level and five agency-based scientific advisory committees at the second:

> The Advisory Committees were to provide a detailed, scientific review of specific applications submitted to them by any federal agency. The Committees chartered by the FDA, EPA, and USDA were to concern themselves mainly with commercial applications. The NIH RAC was to continue to advise on research involving recombinant DNA, and The National Science Foundation was to charter a Committee to examine potential effects of environmentally related basic research.[272]

The biotechnology science board was to consist of members from each agency-based advisory committee and was to "evaluate the review procedures established by those committees, conduct analyses of issues of broad concern regarding rDNA, rRNA and cell fusion," and develop guidelines and provide a forum for public comment.[273] The board was to report to the Secretary of Health and Human Services; it had substantial power to ensure interagency cooperation and consistency through its review of regulatory procedures in the individual agencies.[274]

In addition, the proposal contained draft policy statements for the regulation of biotechnology by the FDA, the EPA, and the USDA. These policy statements did not describe regulatory requirements "but rather the general policy framework within which regulatory decisions" would be made by each of the agencies.[275]

In its policy statement the FDA noted its extensive experience with the application of its regulations to the products of biotechnological processes, both new and old. Thus, the agency proposed no new procedures or requirements for biotechnology products under its jurisdiction. The FDA's overriding policy was that regulation must be based on a case-by-case scientific evaluation of products and not on assumptions about certain technological processes.[276]

The EPA's policy statement addressed the regulation of genetically-engineered organisms under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA). The EPA re-articulated its intent to apply TSCA to genetically engineered orga-

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271. Isakoff, *supra* note 42, at 25.

272. *Id.*

273. *Id.*

274. Note, *Rutabaga*, *supra* note 15, at 1542.

275. *Proposal for a Coordinated Framework for Regulation of Biotechnology*, 49 Fed. Reg. 50,856 (1984).

276. *See* SUBCOMM. REPORT, *supra* note 14, at 12.

nisms[277] and began to develop a regulatory policy directed to that goal and to address some of the weaknesses of the regulatory system described earlier. For example, the EPA recognized that information required in a PMN for non-microbial chemical substances might not be adequate for genetically engineered microorganisms, and stated its plan to set forth the PMN requirements for these microorganisms on a case-by-case basis. The EPA also stated its intent to eliminate the small quantity research and development exemption for field tests of genetically altered microorganisms and to consider the adoption of new SNURs and reporting requirements for microorganisms not subject to the PMN requirements if such organisms posed a risk to human health or the environment.

One of the most difficult issues the EPA faced early on in developing its regulatory policy under TSCA was how to apply the definition of a "new" chemical substance to genetically engineered organisms. Under TSCA a chemical substance manufactured for commercial purposes that is not either listed by name on the chemical substances inventory or "naturally occurring" is "new" and subject to the PMN requirements prior to manufacturing.[278] The difficulty arises in distinguishing certain biotechnology-derived substances from naturally occurring substances. In its 1984 policy statement, the EPA attempted to distinguish between a "new" substance and a "naturally occurring" one by means of the degree of "human intervention" involved in creating the substance. Naturally occurring substances were those that existed as a result of natural events or processes, or as a result of "limited manipulation of natural processes."[279] Substances created by R-DNA, R-RNA or cell fusion were considered non-naturally occurring and subject to PMN, while those created by selection were considered naturally occurring and exempt from the PMN requirements.

Under FIFRA the EPA also responded to earlier criticisms of its regulatory framework. For example, the EPA adopted a "process-based" review of new pesticides, imposing different testing requirements for registration of non-indigenous and genetically-engineered microbial pesticides than for registration of indigenous microbial pesticides.[280] In addition, once an application for registration of such a pesticide was received, additional data requirements would be determined on a case-by-case basis, "depending on the particular microorganism, its parent microorganism, the pesticide use pattern, and the manner and extent to which the microorganism has been altered/manipulated."[281] Supplementary data requirements could include information on the "control region of the genes being altered in the

277. *Proposal for a Coordinated Framework for Regulation of Biotechnology*, 49 Fed. Reg. 50,886 (1984).

278. *Id.* at 50,887.

279. *Id.* at 50,888.

280. *Id.* at 50,884.

281. *Id.*

biotechnology process, a description of the new traits or characteristics the genetic manipulation was intended to cause, tests to evaluate genetic stability and exchange, and selected environmental and toxicology tests."[282] Furthermore, the EPA adopted the "interim" policy that an experimental use permit would be required for all field tests of non-indigenous and genetically-engineered microbial pesticides.[283] In its 1984 statement the EPA did not mention any other environmental statutes as bases for its regulation of biotechnology.

The USDA expressed its view that its existing regulatory framework combined with the NIH *Guidelines* was adequate for the regulation of agriculture-related biotechnology research and product development. Furthermore, the USDA stated that it had "endorsed and adopted the NIH Guidelines for Research Involving Recombinant DNA molecules for coordinating interagency research review, and established an internal policy requiring compliance with these guidelines as a condition for receiving funds for research."[284]

The OSTP received numerous comments on the proposed framework most of which attacked the two-tiered review process as "cumbersome and unnecessary."[285] Industry representatives, in particular, feared that a review board would add an additional hurdle to the regulatory process.[286] In response, the OSTP issued a revised version of the coordinated framework on November 14, 1985,[287] replacing the BSB with the Biotechnology Science Coordinating Committee (BSCC). The BSCC, consisting of representatives from the NIH, the EPA, the NSF, the FDA, and the USDA, was to have four functions:

> to coordinate scientific information sharing and problem solving; to promote the development of consistent review procedures and assessment techniques by affected agencies; to foster agency cooperation on new scientific issues; and to identify important gaps in scientific understanding of rDNA. In short, the BSCC [would] not oversee the individual agen-

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282. Kriz, *supra* note 93, at 395.

283. *See Proposal for a Coordinated Framework for Regulation of Biotechnology*, 49 Fed. Reg. 50,880 (1984). In taking this action the

> EPA cited the possibility that microbial pesticides might replicate and spread beyond the site of application. The agency also said that there may not be natural control or dissipation mechanisms to which the non-indigenous and genetically engineered microbial pesticides would be subject. Therefore, the agency believed that small-scale tests with microbial pesticides could raise potential environmental issues comparable to those of large-scale tests of conventional chemicals.

J. GIBBS, *supra* note 77, at 15.

284. *Proposal for a Coordinated Framework for Regulation of Biotechnology*, 49 Fed. Reg. 50,898 (1984).

285. Note, *Rutabaga*, *supra* note 15, at 1542.

286. *Id.* at 1542 n.86.

287. *See Coordinated Framework for Regulation of Biotechnology: Establishment of the Biotechnology Science Coordinating Committee*, 50 Fed. Reg. 47,174 (1985).