

# Regulatory Oversight of Genetically Engineered Microorganisms: Has Regulation Inhibited Innovation?

ROGER P. WRUBEL<sup>1</sup>\*

SHELDON KRIMSKY

Department of Urban and Environmental Policy

Tufts University

Medford, Massachusetts 02155, USA

MOLLY D. ANDERSON

School of Nutrition Science & Policy

Tufts University

Medford, Massachusetts 02155, USA

**ABSTRACT** / Using detailed interviews with company representatives and researchers in the field, this paper examines

the factors that might account for the slow pace of development of genetically engineered microorganisms (GEMs) intended for environmental release. We specifically analyzed the role of the regulatory system in shaping innovation. We identified at least two cases where industry decided to discontinue the development of a genetically engineered microbial product because of concerns over regulatory oversight. However, most often industry decisions to continue or halt development of GEMs were based on an evaluation of the particular product's efficacy and potential for profitability. Thus the inability of GEMs to perform up to expectations in the field, rather than the regulatory constraints, appears to be the factor responsible for the slow pace of development.

The influence of government regulation on innovation in agricultural and environmental biotechnology has been a topic of intense debate since the first attempt to field test the "ice-minus" bacteria in California in 1983 (Marx 1987, Krimsky and Plough 1988, Krimsky 1991). Unlike most pharmaceutical and industrial uses of biotechnology, agricultural and environmental applications usually require release of the genetically engineered organisms (GEOs) into the environment. Even in closely monitored field tests, the probability of escape of GEOs can never be reduced to zero. In part because of the perceived uncertainty associated with the safety of the environmental release of plants and microorganisms created through genetic engineering, in 1986 the federal government in the United States created a framework of regulation. Some observers have asserted that investment, research, and innovation in agricultural and environmental biotechnology have been discouraged by overregulation or by the failure of regulatory agencies to provide clear guidelines covering the environmental release of GEOs (Naj 1989, Tolin and Vidaver 1989, Brill 1991, Miller 1991, 1995a,b). In a

survey conducted in 1989, 16% of academic and 23% of private industry respondents indicated they were discouraged by government regulatory policy from conducting field trials with genetically modified organisms (Ratner 1990). One critic of the current biotechnology regulatory system in the United States charged that the US Department of Agriculture and the Environmental Protection Agency "have built huge, expensive, and gratuitous biotechnology regulatory empires preoccupied with negligible-risk activities, and have succeeded in protecting consumers only from enjoying the benefits of the new technology" (Miller 1993, p. 1076).

The new tools of biotechnology, especially recombinant DNA techniques developed over the past 20 years, have been used to increase the effectiveness of microorganisms already in commercial use or to create new types of potentially useful but previously unexploited microbes. Bacteria, viruses, and fungi have been modified by recombinant DNA techniques to: enhance the nitrogen-fixing capability of legumes (Cannon and others 1988, Ronson and others 1990), make crop plants more tolerant to yield reducing abiotic stresses (Lindow 1987, 1990a), control insect pests and pathogens of agricultural crops (Kirschbaum 1985, Obukowicz and others 1986, Bishop and others 1988, Wood and Granados 1991, Tomalski and Miller 1991, McCutchen and others 1991, Bonning and Hammock 1992), degrade toxic chemicals (Friello and others 1976, Ramos and others 1987, 1991, Rojo and others 1987, Mondello 1989, Short and others 1990), protect wildlife from

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<sup>1</sup>Present address: Undergraduate Environmental Studies Program, UMASS/Boston, 100 Morrissey Blvd., Boston, Massachusetts 02125-3393, USA.

\*Author to whom correspondence should be addressed.

disease (Rupprecht and others 1986), biologically control vertebrate populations (Morell 1993), and ameliorate plant diseases (Choi and Nuss 1992). Genetically engineered microorganisms (GEMs) have also been proposed for use in the mining industry as bioaccumulators of valuable heavy metals and for efficient and environmentally friendly bioprocessing of minerals (Curtis 1988, Lindow and others 1989, Goldstein and others 1993, Moffat 1994). A number of products, including enzymes and hormones for food production and processing, utilizing GEMs in contained fermentation processes, have already been commercialized (Wrage 1994, 1995). In contrast, while many agricultural and environmental applications of GEMs have been suggested (e.g., Lindow and others 1989, Office of Technology Assessment 1991, Berry and Hagedorn 1991), and while there has been a high level of activity in laboratory research, surprisingly few field tests have been conducted in the United States. Only three types of products have thus far been commercialized: "killed" bacteria genetically engineered to contain an insect toxin (Fischer 1991), a live recombinant virus to control rabies in wildlife (J. Maki, Rhone-Merieux, Athens, Georgia, USA, 1995, personal communication); and bacteria that recombine genes among different strains of *Bacillus thuringiensis* (*Bt*) to improve insecticidal performance (J. Baum, Ecogen, Langhorne, Pennsylvania, USA, 1996, personal communication).

The first attempt to field test GEMs was met with public apprehension, intense media attention, and caution mixed with indecision on the part of regulatory agencies (Krimsky 1991). In contrast, the first field tests of transgenic plants, conducted at the same time, proceeded uneventfully without much public or media notice. Why was there such a difference in response to the two types of releases, when the possibility of serious adverse environmental impacts had been postulated for both? Three factors help explain the contrasting response. First, our understanding of the biology and ecology of microorganisms is limited, especially when compared to higher plants and animals. Therefore more uncertainty is associated with predicting the likelihood of unintended and unwanted effects from field tests of GEMs. Second, unlike field tests of transgenic plants, even small scale field releases of GEMs are difficult to contain. Once released, retrieval of GEMs is essentially impossible. Third, GEMs potentially can exchange genetic material with unrelated indigenous microbes through horizontal transfer. Thus, the possibility of gene movement after release of GEMs can never be completely excluded (Comeaux and others 1990). As far as we know, this type of nonsexual horizontal

transfer of genes has never been demonstrated in plants.

A comparison of the number of field tests of genetically engineered plants and genetically engineered microorganisms conducted in the United States is striking. While over 2500 field releases of genetically engineered plants have been conducted, fewer than 100 field releases of genetically engineered microorganisms have been carried out. Fourteen genetically engineered crops have been commercialized with many others nearing approval. In contrast, only three types of genetically engineered microbial products requiring environmental release have been commercialized. Furthermore, there are very few GEMs waiting in the wings for approval. From these data one might conclude that plant biotechnology was progressing, albeit at a slower pace than some observers would like, but that microbial biotechnology, at least the products requiring environmental release, was stalled. Is a burdensome regulatory system to blame for the disparity?

Uncertainties and public fears might lead regulators to be overly cautious and require extreme prerelease assurance of the safety of releases compared to data required for field tests of transgenic plants. In reviewing the biotechnology literature we found it to be a commonly accepted and unchallenged theme that companies and academic researchers have been deterred from developing GEMs for agricultural and environmental purposes because they are faced with burdensome and unclear regulatory requirements and have no assurances that releases of GEMs they have developed will ultimately be allowed (Tolin and Vidaver 1989, Brill 1991, Faust and Jayaraman 1990, Miller 1991, Shaw and others 1992, Day 1993).

Our objective in this article is to examine the factors that might account for the slow pace of development of GEMs, with the aim of explicating the role of the regulatory system in shaping innovation and affecting the decisions of innovators to proceed with the advancement of new products. To this end we evaluated two competing but nonexclusive hypotheses. First, the regulatory system has inhibited innovation by being too restrictive and placing too many demands on researchers, making them wary they will not be allowed to field test much less commercialize their products; second, technological difficulties amidst unrealistic expectations have resulted in the relatively slow pace of microbial product development.

## Methods

To gain an understanding of the factors that influence the rate of innovation of GEMs for agricultural

and environmental uses, we investigated the research programs, R & D activities, and business decisions of scientists and management personnel involved with the development or commercialization of GEMs. Our research group conducted a survey of personnel at companies and university research laboratories, conducted follow-up interviews from our survey population as well as with several researchers or company representatives suggested to us in the survey responses, used information from prior interviews conducted in 1992 for a related project with representatives of companies developing GEMs, and reviewed the scientific and business literature relevant to the environmental release of GEMs. Drawing on the survey and interview data we obtained from firms that were positioned to exploit the development of GEMs, we evaluated the relative strengths of the hypotheses.

### Survey and Interviews

Companies and university research laboratories working with genetically engineered microorganisms were surveyed in two stages. A list was obtained from the United States Environmental Protection Agency of all applications as of 1 January 1993 for Premanufacture Notifications under the Toxic Substances Control Act and for field release of GEMs intended to be used as pesticides under the Federal Insecticide, Fungicide and Rodenticide Act. Each company or research laboratory on this list was contacted to create a comprehensive set of innovators. This was practical since the number of companies or laboratories working with GEMs intended for environmental release is small. A few additional researchers who are working with GEMs but had not yet made applications for a field release were identified through recommendations of our initial survey participants, from lists of conferees at GEM symposia, through a literature review of biotechnology research, and through contacts made during an earlier project on transgenic organisms.

During the spring of 1993, a four-page questionnaire was sent to scientists or managers in charge of research at 19 different companies and research institutions, asking background information on current research with GEMs and the regulatory status of these projects. Questionnaires were returned by 13 (68%). Follow-up telephone interviews were completed with 11 of these scientists and research managers. Letters were sent asking for specific follow-up information to all contacts on the list who could not be reached for a telephone interview. Supplemental information came from telephone and in-person interviews conducted in 1992 with six additional scientists and research managers developing GEMs. The survey instrument and telephone inter-

views were designed to gain an understanding of the company's commercial interest in GEMs and the obstacles to development. Since the regulation of GEMs is cited as having a significant impact on commercial pursuits (e.g., Tolin and Vidaver 1989, Day 1993, Miller 1993, 1994, 1995a,b), we begin with a brief overview of the regulatory situation.

### Regulatory System for Environmental Release of GEMs

Genetically engineered microorganisms (GEMs) intended for release in US territories fall under the regulatory authority of the United States Environmental Protection Agency (EPA) and the United States Department of Agriculture (USDA). The EPA's authority derives from two acts: the Federal Fungicide, Insecticide and Rodenticide Act (FIFRA) covers all pesticidal uses of GEMs, whereas the Toxic Substances Control Act (TSCA) is designed to screen new chemical substances prior to their introduction into commerce and to regulate both existing and new chemical substances which present an unreasonable risk to health and the environment. The authority under USDA derives principally from the Federal Plant Protection Act and the Plant Quarantine Act.

EPA's statutory authority over GEMs was initially questioned by its own agency (Krimsky 1991, p. 187). However, with increasing pressure from Congress, in 1984 EPA issued a policy statement that "chemical substances" include living organisms, and GEMs fall under TSCA review either as a new chemical substance or as a significant new use of an existing chemical substance (USEPA 1984). Before EPA could undertake a rulemaking action on GEMs under TSCA, it needed to answer three questions: (1) How will new microorganisms be defined? (2) What will count as a "significant new use" of a microorganism? and (3) Would naturally occurring microorganisms ever be considered new?

Two years after EPA's decision to exercise regulatory action on GEMs, the agency defined the term "new chemical substance" for microorganisms as intergeneric microorganisms: microorganisms derived from genetic material of organisms in different genera [OSTP (Office of Science and Technology Policy) 1986, pp. 23313-23349]. Exclusions to the definition of new microorganisms are: (1) naturally occurring microorganisms, (2) genetically modified microorganisms other than intergeneric, and (3) intergeneric microorganisms resulting only from addition of well-characterized noncoding regulatory regions.

The EPA was delayed in receiving Executive Office approval for promulgating draft rules defining registra-

tion procedures for GEMs under FIFRA and TSCA pending publication of the scope principles for biotechnology, eventually released in 1992 (OSTP 1992) after considerable debate. In 1994 EPA issued proposed guidelines for regulating GEMs under TSCA (USEPA 1994a) and final guidelines for use permits and notification procedures under FIFRA (USEPA 1994b).

According to Day (1993), the bioremediation industry has suffered because of the delay in TSCA rulemaking:

The extremely slow progress of USEPA's rule has had a dramatic impact on the commercial development of genetically engineered microorganisms for remediation. . . . Because of the uncertain regulatory costs, the U.S. bioremediation industry has focused on optimizing the use of naturally occurring organisms, thus limiting the commercial development of products that must comply with TSCA [Day 1993, p. 327].

The EPA has authority to issue experimental use permits (EUPs) for the testing of new pesticides or new uses of existing pesticides under FIFRA. In October 1984, EPA issued an interim policy under FIFRA for field tests of microbial pesticides (USEPA 1984). Under this policy the agency required notification prior to all small-scale field tests involving certain microbial pesticides in order to determine whether an EUP was needed. The scope of the policy includes nonindigenous microorganisms and genetically altered or manipulated organisms released into the environment as biological control agents. Under FIFRA, EUPs are generally for large scale (greater than 10 acres of land or any aquatic application to more than 1 surface acre of water) tests. The agency has proposed to amend FIFRA to require notification before initiating small-scale testing of certain microbial pesticides; the new proposed policy, however, limits the scope of notification requirements to a smaller group of pesticides than was defined in the 1986 policy. EPA's currently preferred option requires an EUP for microbial pesticides whose pesticidal properties have been imparted or enhanced by the introduction of genetic material that has been deliberately modified.

In 1986 EPA developed a classification system to distinguish among types of microbial pesticide products and the level of reporting required (OSTP 1986). Level I reporting (30-day agency review) was delegated to low-risk field tests, while level II notification (full 90-day review) was specified for field tests of high potential risk. Higher levels of review are given to intergeneric, nonindigenous, pathogenic organisms based on EPA's view that these products are more likely to exhibit new combinations of traits.

The first GEM regulated under FIFRA and approved for field tests was a strain of *Pseudomonas syringae* with a deletion mutant. Commonly referred to as "ice-minus" because it does not promote ice crystal formation until temperatures of 27°F or lower, the first field tests were carried out in 1987 (Krimsky and Plough 1988, p. 84). The company that holds the current patent for "ice-minus," DNA Plant Technology Corporation, halted research on the genetically engineered strain. Instead it has pursued registration of a naturally occurring *P. syringae* ice-minus mutant for which the regulatory path is less burdensome (Suslow 1992).

The USDA (1993) published a final rule for the introduction of genetically engineered organisms (GEOs). The objective of the USDA rule is to establish notification procedures for field testing, interstate movement, and importation of certain classes of genetically modified organisms. This new rule removes existing requirements that researchers obtain permits from the USDA's Animal and Plant Health Inspection Service (APHIS) before field testing GEOs; instead researchers are required only to notify APHIS of such releases and to certify that introductions of GEOs meet certain performance standards. A new provision of the rule establishes a procedure for exempting organisms entirely from either permit or notification requirements.

Following the Office of Science and Technology Policy scope principles closely, the strategy of the agency is to assess the safety of modifying the hereditary traits of an organism. The USDA regulates microorganisms if they are plant pests. The criteria states that the donor, vector, vector agent, or recipient organisms must belong to a group of organisms designated as a plant pest. Proposed exemptions from USDA guidelines on GEMs are: (1) microorganisms modified solely by chemical or physical mutagenesis, the movement of nucleic acids using physiological processes, or plasmid loss or spontaneous deletion; (2) microorganisms modified by the introduction of noncoding, nonexpressed nucleotide sequences that cause no phenotypic or physiologic changes compared to the parental organism; and (3) specific microorganisms exempted by USDA. The latter exemption might be invoked if the recipient microorganism is nonpathogenic, noninfectious, not a plant pest, resulted from the addition of well-characterized DNA, and is comprised of noncoding regions.

In some instances, certain organisms are subject to joint regulation by USDA and EPA, such as if the GEM is a plant pest and also meets the criteria of being a pesticide or new microorganism under TSCA. The agencies are expected to work cooperatively if a GEM falls within both their statutory jurisdictions.

Table 1. Genetically engineered microorganisms initially field-tested in the US before July 1995<sup>a</sup>

Organism	Date	Type of genetic modification <sup>b</sup>	Purpose of modification	Organization	Current status
<b>Bacteria</b>					
<i>Pseudomonas syringae</i> (ice nucleating bacteria)	1987–1990	Deletion of ice nucleation gene	Frost protection for crops (e.g. strawberry and potato)	Advanced Genetic Sciences (later merged with DNA Plant Technology)	Research discontinued
<i>P. syringae</i> (ice nucleating bacteria)	1987–1990	Deletion of ice nucleation gene	Frost protection for crops	University of California, Berkeley	Basic research on epiphytic ice nucleating bacteria continuing
<i>P. fluorescens</i> (rhizosphere bacteria)	1987	Chromosomal insertion <i>Escherichia coli</i> lac operon genes <i>lacZ</i> and <i>lacY</i> ( <i>lacZY</i> )	Detection of bacteria in field. <i>LacZY</i> is a marker gene, which enables recombinant <i>P. fluorescens</i> , unlike the wild type, to utilize lactose as its sole carbon source; recombinant bacteria can be detected by plating on a lactose-only medium	Monsanto Co./Clemson University	Research discontinued
<i>P. aureofaciens</i> (rhizosphere bacteria)	1988	Insertion of <i>lacZY</i> genes from <i>E. coli</i> into <i>P. aureofaciens</i> . <i>P. aureofaciens</i> is a biotype of <i>P. fluorescens</i> with antifungal properties	Improve efficacy of bacteria for control of take-all disease of wheat and improve detection of the recombinant bacteria in the field	Monsanto Co., Washington State University, Clemson University and USDA-ARS	Research discontinued
<i>P. aureofaciens</i> and <i>P. fluorescens</i> (rhizosphere bacteria)	1990	Insertion of <i>lacZY</i> genes from <i>E. coli</i>	Increase efficacy of bacteria for control of take-all disease of wheat	Monsanto Co., Purdue University, Montana State University, Washington State University	Research discontinued
<i>Clavibacter xyli</i> <i>cynodontis</i> (endophytic bacteria)	1988–1993	Insertion of $\delta$ -endotoxin gene from <i>Bacillus thuringiensis</i>	Control of European corn borer ( <i>Ostrinia nubilalis</i> ) and effect of <i>C. xyli</i> on the crop	Crop Genetics International and USDA-ARS	Research discontinued in 1994
<i>Rhizobium meliloti</i> (soil inhabiting nitrogen-fixing bacteria)	1988–1994	Insertion of a <i>nif</i> promoter gene from <i>Bradyrhizobium japonica</i> and insertion of three <i>dct</i> genes from <i>R. leguminosarum</i>	Increase nitrogen uptake by alfalfa; studies on ecology and behavior of the transgenic organisms	Biotechnica International Inc. (1988–1991)/Research Seeds Inc. (1992–1994)	Strains sold to Research Seeds Inc. in 1991; commercialization request pending at EPA 1995

### History of Field Testing GEMs in the United States

A number of genetically engineered bacteria and viruses have been field-tested in the United States

beginning in 1987 (Drahos 1991a) (Table 1). The first field tests of a GEM were conducted by Advanced Genetic Sciences (AGS) and scientists at the University of California, Berkeley, on the ice-minus strain of *P. syringae*. They were approved after several

Table 1. (Continued)

Organism	Date	Type of genetic modification <sup>b</sup>	Purpose of modification	Organization	Current status
<i>Bradyrhizobium japonica</i> (soil inhabiting nitrogen-fixing bacteria)	1988–1991, 1995	Insertion of <i>nif</i> promoter gene from <i>R. meliloti</i> and <i>dc1</i> genes from <i>R. leguminosarum</i>	Increase nitrogen uptake in soybeans; also studies on ecology and behavior of the transgenic organisms	Biotechnica International Inc. and Louisiana State University (1988–1991), Research Seeds Inc. and University of Wisconsin (1995)	The strains were sold to Research Seeds Inc. in 1991; Research Seeds is not now planning commercialization; strains were used for field tests by University of Wisconsin researchers in 1995
<i>Bacillus thuringiensis kurstaki</i> (soil bacteria)	1990–1994	Insertion of $\delta$ -endotoxin gene from <i>B. thuringiensis wuhanensis</i>	Improve efficacy for control of caterpillars	Sandoz Agro Inc.	Field tests continuing with goal of commercialization
<i>Bacillus thuringiensis kurstaki</i>	1992–1994	Insertion of $\delta$ -endotoxin gene from <i>B. thuringiensis kumamotoensis</i>	Create a new strain for control of Colorado potato beetle	Ecogen Inc.	Approved by EPA January 1995; product name: Raven
<i>Bacillus thuringiensis kurstaki</i>	1992–1996	Insertion of $\delta$ -endotoxin gene from <i>B. thuringiensis aizawai</i>	Improve host range and efficacy for control of caterpillars	Ecogen Inc.	Bioinsecticide Approved by EPA February 1996; product name: Crymax
<i>Bacillus thuringiensis kurstaki</i>	1994–1996	Insertion of $\delta$ -endotoxin gene from <i>B. thuringiensis aizawai</i>	Increase yield of active ingredient during fermentation process	Ecogen Inc.	Bioinsecticide Pending approval
<b>Viruses</b>					
<i>Autographa californica</i> nuclear polyhedrosis virus (lepidopteran pathogen)	1989	Deletion of polyhedrosis gene	Limit the persistence of a recombinant virus in the environment to assure safety of releases	Boyce Thompson Institute for Plant Research	Field work continued by AgriVirion Inc. (see below)
<i>Orthopox vaccinia</i> (pox virus)	1990–1995	Insertion of glycoprotein gene from <i>Lyssavirus rabies</i> (rabies virus)	Vaccine for wildlife rabies	Rhone-Merieux Inc. and Wistar Institute	Rhone-Merieux Inc. issued conditional license for use and sale of vaccine April 1995–April 1996
<i>Lymantria dispar</i> nuclear polyhedrosis virus (gypsy moth pathogen)	1993	Deletion of polyhedrosis gene, insertion of <i>lacZ</i> gene from <i>E. coli</i>	Determine persistence and track movement in field	Boyce Thompson Institute for Plant Research	Monitoring of site continuing, to track virus through 1995; no commercial value at this time

years of controversy and five years of regulatory review (Krimsky 1991). The ice-minus bacteria were considered generally to be low risk because the modification involved a gene deletion rather than the addition of a new gene and the ice-minus strain is found as a

naturally occurring mutant in the habitat into which it was released. The first release of a genetically engineered virus in 1989 also involved a gene deletion and raised little concern among regulators or the public.

Table 1. (Continued)

Organism	Date	Type of genetic modification <sup>b</sup>	Purpose of modification	Organization	Current status
<i>Autographa californica</i> nuclear polyhedrosis virus (lepidopteran pathogen)	1993–1994	Deletion of polyhedrosis gene	Determine infectivity and persistence of mutant virus for control of <i>Trichoplusia ni</i> (cabbage looper). Goal is to develop a virus that will die off soon after the infected insect dies. Then insect-specific toxin genes could be inserted into the virus without the risk of unwanted toxicity to non-target insects.	AgriVirion Inc.	Research continuing
<i>Autographa californica</i> nuclear polyhedrosis virus (lepidopteran pathogen)	1993–1995	Deletion of <i>egt</i> gene of virus; this gene prevents the host insect from molting and pupating; insertion of scorpion venom gene	Improve efficacy of virus for control of caterpillars. Deletion of the <i>egt</i> gene from the virus to make caterpillar cease feeding quickly after infection. Insertion of a scorpion venom gene to kill the caterpillar more quickly than the wild type virus.	American Cyanamid	Research continuing

<sup>a</sup>Data from Drahos (1991a) and compiled by authors.

<sup>b</sup>Donors of marker genes (e.g., lac operon genes or antibiotic resistance genes) are only reported when the primary purpose of the field release was to determine the effectiveness of the marker.

<sup>c</sup>*Nif* genes activate the production of nitrogenase an enzyme required for symbiotic nitrogen fixation and *det* genes express enzymes for the transport of C<sub>4</sub>-dicarboxylic acids, an energy source for the nitrogen fixation reactions.

Several of the projects listed in Table 1 have been discontinued. Researchers at DNA Plant Technology (DNAP and AGS merged in 1989) discovered naturally occurring strains of *P. syringae* that lacked ice nucleating genes and were as effective in inhibiting ice formation on plants as the genetically engineered strain (Suslow 1992). DNAP decided to pursue field testing of the naturally occurring strains and delay further development of the genetically engineered strains. Company officials feared that continued regulatory and community-level difficulties regarding genetically engineered microbes, especially pertaining to large-scale testing, would make genetically engineered strains more costly to develop compared to naturally occurring strains (Suslow 1993). DNAP registered the naturally occurring *P. syringae* strains under the name Frostban in 1992.

A major research effort was carried out by the Monsanto Agricultural Company, along with several university and USDA collaborators, to develop pseudomonad strains for control of root diseases. The project was discontinued in 1991 after several years of field testing. As part of this research program, the *E. coli lacZY* system for marking and monitoring microorganisms in the environment was developed and continues to be widely used in microbial research (Drahos and others 1988, Drahos 1991b).

Several other projects initiated by Monsanto were terminated before any field tests were conducted. In 1985 Monsanto applied for a permit to field test a root-colonizing recombinant *P. fluorescens* that incorporated  $\delta$ -endotoxin genes from *B. thuringiensis* for control of root-feeding caterpillars (Obukowicz and others

1986). EPA raised a number of risk concerns (Akcakaya and Ginzburg 1991). Tests had shown that bacteria isolated from infected insects were capable of infecting other insects. This could be viewed as a desirable characteristic in a pest control agent since the infection could spread through the pest population. However, it raises the possibility that the recombinant bacteria would colonize wild plant species and kill nontarget insects, leading to unintended, undesirable, and perhaps unpredictable and uncontrollable ecological effects. There was also concern that the recombinant bacteria would be able to colonize above ground plant parts as well as plant roots, with the risk of uncontrolled spread of the organism. Monsanto was required to repeat some of its greenhouse experiments and provide additional information on the biological and ecological characteristics of the recombinant bacteria. The field test was never conducted and eventually the project was discontinued.

Monsanto also created transgenic strains of *P. corrugata* incorporating the *lacZ* and *lacY* genes of *E. coli*. *P. corrugata* was isolated in Australia and was found to protect wheat from take-all disease, a fungus that attacks plant roots. Because another strain of *P. corrugata* was listed as a mild pathogen of onion and the strain with which Monsanto was working was isolated in Australia, the regulatory agencies listed the recombinant as a "genetically engineered exotic pathogen." Rather than risk a long delay in gaining regulatory approval for a field test, Monsanto decided to terminate this project (Drahoš 1993).

Monsanto eventually abandoned its entire recombinant microbial research program in favor of concentrating its efforts on development of genetically engineered plants, where results indicated a greater potential for commercially successful products (R. Stonard, Monsanto, St. Louis, Missouri, USA, 1992, personal communication). It seems reasonable to speculate that Monsanto's difficulties in getting regulatory approval to field test some of its strains influenced their decision to eliminate the microbial program, although we have found no direct evidence of this. It is also possible that other factors known to decision makers within the company, such as the lack of proven efficacy of the microorganisms being developed or the uncertainty of generating commercially viable products, may have influenced the final demise of Monsanto's program.

From 1988 through 1993, Crop Genetics International (CGI) field tested the endophytic bacteria *Clavibacter xyli cynodontis* with an inserted  $\delta$ -endotoxin gene from *B. thuringiensis* for control of the European corn borer (*Ostrinia nubilalis*) (Dimock and others 1989). While approval of the early field tests required about

one year, more recent field tests were approved in 90–120 days (Davis 1993). Results in 1993 showed that the genetically engineered bacterium was effective in killing up to 80% of the European corn borers attacking corn plants. However, even at this level of control, no yield advantage was observed in protected test plants compared to unprotected controls (Davis 1993). Either the 20% of corn borers remaining, the endophyte itself, or some combination of factors was believed responsible for the yield losses in the insect-protected crop (Davis 1993). In any case, CGI has stopped research and development on the project and has no plans for further field tests or commercialization of this product. Company officials noted that the decision to terminate the project was based on the disappointing field results in 1993 and not on regulatory concerns.

Recombinant strains of *Rhizobium meliloti* engineered to increase nitrogen fixation and increase yields in alfalfa were first field tested in 1988 by Biotechnica International. Field tests have continued each year since then even when the project was taken over by Research Seeds Inc. in 1991. Between 1988 and 1993 Biotechnica and Research Seeds requested and received from EPA approval for 12 field tests under the regulatory authority of TSCA. Following a test market exemption granted to Research Seeds by EPA in 1994, recombinant nitrogen-fixing bacteria were distributed to a selected group of cooperating farmers for on-farm trials. EPA is now considering the company's request for commercial approval of recombinant *R. meliloti* for alfalfa.

Research Seeds also bought from Biotechnica International enhanced strains of *Bradyrhizobium japonica* as an inoculant for soybean. The company determined that the demonstrable soybean yield advantage with the application of economically feasible rates of the recombinant nitrogen-fixing strains was questionable and is not directly pursuing commercial development at the present time (Wacek 1993).

Sandoz Agro has been field testing recombinant *B. thuringiensis kurstaki* since 1990. A new strain has been engineered to contain  $\delta$ -endotoxin genes from another *Bt* strain, *wuhanensis*. Most recently field releases have been conducted in Mississippi and California for control of armyworm in tomatoes and alfalfa. Company officials indicated no difficulty in getting EPA approval for field tests (Sandmeier 1992). The company believes that regulatory officials view these recombinant bacteria as low-risk because the genetic constructs are all derived from the same species, and because *B. thuringiensis* is a well-characterized bacteria that has been used as a biopesticide for insect control since the 1950s. Sandoz Agro has an extended permit from EPA to field test any

combination of registered *Bt* strains. As long as the strains are registered, EPA approval for field tests is not required (R. Sandmeier, Sandoz Agro, Palo Alto, California, USA, 1995, personal communication). Ecogen, Inc., a biopesticide firm in Langhorne, Pennsylvania, USA, has had experiences with EPA similar to Sandoz Agro's. In 1992 Ecogen received blanket approval from EPA for testing recombinant *Bt* strains, created by combining genes from EPA-registered *Bt* strains.

There have been several field tests of genetically engineered baculoviruses. Because the pathogenicity of baculoviruses is limited to specific groups of insects they are considered excellent biological control candidates. However, wild-type baculoviruses kill their insect hosts slowly, which has limited their commercial success. Researchers have been trying to improve the effectiveness of baculoviruses for insect pest control by inserting genes expressing insect toxins.

The host range of baculoviruses is determined by the number of insect species that show disease symptoms. The host range of a baculovirus may be greater than is now known, if the virus infects other insect species without causing disease symptoms (Wood and Hughes 1993). If this is the case, a recombinant baculovirus expressing a generalized invertebrate toxin, such as scorpion venom or  $\delta$ -endotoxin from *Bt*, might harm nontarget beneficial organisms. If recombinant viruses were known to have limited persistence in the environment, then fears that the pathogen might spread out of control could be allayed.

The Boyce Thompson Institute for Plant Research (BTI) conducted field tests on genetically engineered viruses designed for the biological control of caterpillars in 1989 [*Autographa californica* nuclear polyhedrosis virus (AcNPV)] and 1993 [*Lymantria dispar* nuclear polyhedrosis virus (LdNPV)]. Two field tests of AcNPV were conducted by AgriVirion in 1994. Genetic engineering techniques were used to delete a polyhedrosis gene, which enables the assembly of a protein coat around the virus genetic material inside an infected insect. The major goal of this strategy is to create a virus with limited viability in the environment. The protein coat protects the virus when it is outside its host. Unprotected virus particles would likely die shortly after the insect host has died. The research director of these projects indicated that he found regulators to be reasonable and encouraging of the project and that there have been no delays due to regulatory intervention (Wood 1993).

American Cyanamid conducted a field test in 1993 of a AcNPV with a gene disabled (*egt*) that normally functions to prevent infected insects from molting (O'Reilly and Miller 1991). The disabling of this virus

Table 2. Data requirements of companies applying to regulatory agencies for field tests of GEMs

Research organization	Data submitted to regulatory agencies for field tests of GEMs
Biotechnica Int'l	1, 2, 3, 4, 5, 6, 7, 8 <sup>a</sup>
CGI	1, 2, 3, 4, 5, 6, 7, 8
Monsanto	1, 2, 3, 5, 7, 8
Sandoz Agro	1
Boyce Thompson/AgriVirion	1, 7, 8 <sup>b</sup>
AGS/DNAP	1, 2, 3, 5, 6, 7, 8

<sup>a</sup>1: Characterization of the genetic changes and evidence that the recombinant organisms differ from the parental organism only for the intended genes. 2: Genetic stability of the recombinant genes so that the genes would not be shed into the environment once organisms were released. 3: Methods to monitor the organisms during the field test. Use of marker genes and selective media to recover the organisms. 4: Genetic exchange with other microorganisms: Exchange between recombinant and wild-type microbes, between GEM and other types of microorganism. 5: Transport and spread of GEMs: through the air, soil or water; by animal vectors, other microorganisms, or mechanical transfer (e.g., on farm tools). 6: Competition between GEMs and wild types and between GEM and other microorganisms. 7: Persistence in soil, water, on leaves, and on roots. 8: Effects on nontarget organisms: host range studies, toxicity tests.

<sup>b</sup>Studies were not required by regulatory agencies but carried out by researchers.

gene is intended to cause the insect to stop feeding and die more quickly than an insect infected with a wild-type virus. In November 1994 American Cyanamid requested EPA approval to field test an AcNPV virus with a disabled *egt* gene and an inserted scorpion venom gene. Approval was granted and the test was initiated in 1995. In 1996, the company was allowed by EPA to conduct additional field tests on the genetically engineered AcNPV in 12 states.

## Industry Experience with Regulatory Process

### Data Requirements and Costs

Companies that sought approval to field test the first GEMs were required to generate large data sets and devote significant time and resources to satisfy (and sometimes fail to satisfy) regulators. The basic data requirements asked of all applicants for field tests conducted to date include: evidence that the only difference between the parental and recombinant organisms is in the intended genetic changes, evidence that the genetic transformation is stable, and development of methods to monitor the released GEMs in the environment (Table 2).

While researchers were required to track genetically engineered microorganisms after a release to deter-

mine persistence and dispersal, monitoring requirements have decreased over time. The early releases of ice-minus involved very elaborate long-term monitoring of soil, air, water, and plants at and around the test site (Table 2) (Lindow 1990b). Similarly the initial releases of recombinant nitrogen-fixing bacteria and pseudomonads containing marker genes required long-term monitoring for survival and transport of the organisms (Hankinson 1992, 1993, Drahos and others 1988, Drahos 1993).

Following the initial releases of the ice-minus bacteria, the monitoring data were analyzed and showed little risk involved. Numerous field tests were then conducted with substantially relaxed monitoring requirements (Susslow 1992). More recent releases of recombinant *B. thuringiensis* and genetically engineered viruses required some monitoring but far less than demanded in earlier experiments (Sandmeier 1992, Wood 1993).

Data on the effects of the GEMs on their target organisms and nontarget organisms were required in some but not in all cases (Table 2). Not all researchers were asked to evaluate the host range of the recombinant organisms and possible host shifts, exchange of genetic material with other organisms, and competitive effects with other microbes.

Each application is evaluated on a case-by-case basis, so requirements may be imposed based on the unique characteristics of the organism and potential risk factors. For example, when it was found that *C. xyli* could survive on and spread from farm implements, CGI was required to disinfect all farm equipment used in its field tests.

CGI spent three years doing basic research on the ecology and behavior of nonrecombinant *C. xyli* before it requested the first field test of the recombinant bacteria (Carlson 1992). The biology of the parent organism, *C. xyli*, a pathogen of bermudagrass, was not well known at the time. In the early years of development CGI's data collection for regulatory purposes constituted about 30% of the project's research budget. In 1993, expenditures to satisfy regulatory requirements for current projects represent about 15% of the company's research budget (Davis 1993). The time required to gain regulatory approval for field tests is now about 120 days, which is much less than what was needed for the early tests (Davis 1993).

According to one scientist-industry consultant, data collected for prerelease regulatory approval and postrelease monitoring of the early field tests of *R. meliloti* and *B. japonica*, required by the EPA permit, filled nine or ten large binders and consumed up to 50% of the project's resources (Hankinson 1993). Much of the effort went into a comprehensive microbiological moni-

toring program to establish behavior, persistence, and movement of the GEMs over time (Ronson and others 1990). Recent field tests conducted by Research Seeds on *R. meliloti* have been approved within 90 days and regulatory costs have declined to about 10% of budget (Hankinson 1993). EPA is also proposing further relaxation of requirements by exempting tests of *Rhizobium* strains under 10 acres (USEPA 1994a).

Regulatory costs incurred by Monsanto for the research on *P. fluorescens* and *P. aureofaciens* were about 15% of the research budget (Drahos 1993). Regulatory approval for field tests on the *lacZY* strains took about seven months in 1988. This is in contrast to the multiyear requirements to initiate field tests on AGS's ice-minus bacteria and Biotechnica's nitrogen-fixing bacteria. The field tests involving pseudomonads also required large volumes of research data for regulatory evaluation (Drahos 1993). At SBP Technologies, which was developing pseudomonads for bioremediation, estimated spending for regulatory data collection was 5% of the research budget, and the company believed it could obtain regulatory approval for field tests from EPA within 90 days of submission of a premanufacture notice (Drahos 1993).

The costs associated with meeting regulatory standards of the entomophagous virus work at BTI and AgriVirion are estimated at 2% of budget (Wood 1993). The first field test of AcNPV in 1989 occurred less than one year after initial contact with EPA. Subsequent field tests of AcNPV in 1989 and 1993 and LdNPV in 1993 were permitted within 90 days of submission of the request (Wood 1993).

Reductions in regulatory costs for ongoing GEM research compared to those reported for the earlier projects were confirmed for other companies. For example, in 1993 American Cyanamid estimated that current regulatory costs are 1% of its research budget (Ciarlante 1993).

We found that researchers who had gone through the regulatory process initially perceived regulatory requirements as costly, time consuming, and burdensome. However, regulators used the data obtained in early tests to streamline the system, eventually lowering data collection requirements and costs for the next generation of products. Companies testing new recombinant microorganisms whose parent and/or donor strains are well known to regulators from prior tests have benefitted in expedited reviews of applications and reduced data requirements. For example, representatives of Sandoz Agro stated that the large existing data base on the ecology and behavior of *B. thuringiensis* resulted in fewer risk questions that needed to be addressed before field testing was approved (Sandmeier

1992). Ecogen, also working with *B. thuringiensis* did not feel encumbered in conducting field tests and has had two genetically engineered *Bt* strains registered with EPA for commercial sale. The first, an insecticide for control of Colorado potato beetle, was approved one year after submission, and the second, an insecticide for caterpillars, was approved in less than ten months in early 1996, a period which included an extended government shutdown (Table 1) (J. Baum 1996, personal communication).

However, researchers working with novel constructs involving microorganisms that are not well known and for which field data do not exist still have to develop the basic biological and ecological data to enable regulators to adequately assess the risks posed by the releases.

#### Usefulness of Regulatory Approval Data for Research Purposes

Estimates of the costs of regulatory compliance presuppose that the data generated for regulators have no benefit to the creation of new products. The primary concern of the researchers is determining how well the GEM performs in the field. Ecological questions pertaining to risk, such as the likelihood of gene transfer to other microorganisms and the probability of transport of the GEM out of the test site, are of primary interest to regulators. However, questions of persistence and competitiveness of the GEMs may be of common interest to both regulators and companies.

One of the major problems companies have encountered in constructing effective GEMs is the difficulty of securing survival of sufficient numbers of organisms upon field release. Detailed studies of the persistence and competitiveness of the nitrogen-fixing GEMs released by Biotechnica and later by Research Seeds revealed that favorable greenhouse experiments on sterile soil in which treatment of seeds with the GEMs resulted in greatly increased plant biomass were not replicated in field tests. Data required by regulators on persistence and competitiveness of the GEMs during field tests indicated that the GEMs were not good competitors with indigenous soil microbes. Less efficient indigenous nitrogen-fixers outcompeted the genetically modified ones for nodulation sites on the plant roots. Researchers at Biotechnica then attempted additional genetic alterations of the GEMs that would increase their competitiveness in the field.

At CGI, where much effort was spent developing a data base on the largely unknown *C. xyli* bacteria, research revealed that one of the primary advantages of employing endophytes over other microorganisms is that they stay where you put them (Carlson 1992). Encouraged by this result, company researchers began

considering the recombinant *C. xyli/Bt* bacteria as a pest control tool.

Researchers at BTI reported that data requests by regulators for field tests of genetically engineered viruses were reasonable and not burdensome (Wood 1993). They perceived that regulators were interested primarily in determining whether the correct genetic changes had been made and whether the viruses carried any unintended modifications. Because the viruses and genes used by BTI were well characterized, it was not technically difficult to provide evidence that satisfied regulators. BTI is now pursuing independent research into other areas that include identification of host ranges for entomopathic viruses, persistence of viruses in the environment, and genetic exchange between viruses (Wood 1993). While these data were not requested by the regulatory agency for the releases proposed by BTI, they are of biological interest for commercialization and are likely to be included in future risk assessments.

#### Industry Attitudes Regarding Regulatory Process

In the view of one industry executive, regulation is simply one of many business concerns that must be addressed in successfully commercializing a product, no less than marketing and manufacturing. Many of the researchers and company representatives interviewed for this study described themselves as supporting regulation for two reasons: first, it insures that industry carefully considers the safety of products being developed in addition to the profit potential; second, regulation assures the public that products being tested and eventually marketed have been evaluated for safe use. All of the researchers and company representatives surveyed and interviewed believed that the GEMs they were developing presented no significant environmental and health risks. Several researchers believed that genetic changes made to microorganisms render them less competitive with the parental strains (Cassin 1993, Tiedje 1992).

The most serious challenge cited was creating GEMs with sufficient competitiveness, vis-à-vis indigenous microorganisms, to survive long enough in the environment to be effective. At the same time, several researchers stated that all GEMs should be disabled in some way to eliminate the possibility that a deleterious organism would persist (Wood 1993, Cassin 1993). While believing that regulation was necessary, many researchers feared that regulators may sometimes make excessive demands that are not justified by the potential risk of the GEM. This feeling was especially strong among the researchers who had been involved in the first releases of GEMs.

Representatives of companies that were developing GEMs but had not field tested them expressed uncertainty over how difficult it would be to go through the approval process. At American Cyanamid, researchers working on genetically engineered entomopathogenic viruses were uncertain how difficult it would be to get approval for environmental releases because few GEMs had been tested. According to one industry scientist, companies developing GEMs for bioremediation have benefitted from the experience that the regulatory agencies are acquiring in dealing with field tests of GEMs mainly for agricultural uses. He suggested that by the time GEMs for bioremediation are ready for field testing, the regulatory situation may be sorted out (Cassin 1993).

The regulatory framework was also seen by almost all the company representatives interviewed as an essential part of improving the public image of biotechnology. For example, while some researchers believed that the permit requirement for very small acreage tests discriminated unfairly against biotechnology, one industry executive commented that in this early stage of the technology such extra precautions are worth having because they improve public confidence. In most cases, the researchers and other industry representatives spoke of the regulatory framework as a constructive rather than an antagonistic force. Some researchers decried attempts to short-circuit the existing data requirements. The consensus among those we interviewed was that even if some data requirements appear to be excessive, prompt compliance is in order. Cooperation is rationalized by its strategic or political advantages, even when scientific advantages are questionable.

#### Technical Problems Versus Regulatory Concerns Affecting Industry Development Decisions of GEMs

Our research indicates that in at least two cases, industry decisions to discontinue the development of a genetically engineered microbial product were based on concerns over regulatory oversight that was likely to cause delays and possible prohibition of large scale releases. Both of these products were among the first to be developed by industry. Most often industry decisions regarding the continued development of GEMs were and continue to be based on an analysis of a product's efficacy and potential profitability.

Fears that large-scale field tests and eventual commercialization might lead to regulatory and public opposition clearly influenced DNAP's decision to discontinue its research into recombinant bacteria for frost protection. However, other factors also came into play. DNAP's research emphasizes the use of genetic engineering for

improvement of the quality of vegetables. A plant protection product for frost tolerance, inherited in the merger with AGS, did not fit well with the company's marketing goals (Suslow 1992). In addition, company researchers discovered naturally occurring bacteria that were as capable of providing frost protection as the genetically engineered strains. These naturally occurring strains were commercialized in 1992.

Monsanto's decision to discontinue its microbial research program was based, in part, on the prospect of regulatory delays in field testing its intergeneric bacteria. However, the company's analysis of the commercial potential of the GEM products compared to its transgenic plant products, which were further along in development, probably also motivated discontinuance of its microbial research effort. Because field tests of recombinant pseudomonads carrying insecticidal genes were never conducted, their efficacy was never established. It is possible that no one has followed up on this product because of doubts about its effectiveness in the field and its long-term economic potential. Monsanto has shown a willingness to confront regulatory hurdles and aggressively respond to public opposition to its genetically engineered products, for example, bovine growth hormone, when it sees a profitable marketing opportunity.

CGI's decision to discontinue testing of its recombinant endophytic insecticide is clearly based on disappointing results from field tests. There has been no public opposition to its field tests, and the company had developed significant data that would have likely made regulatory approval for commercialization noncontroversial.

Biotechnica International decided to sell its enhanced genetically engineered rhizobia strains because the company lost confidence in the profit potential of its nitrogen-fixing organisms. Field tests conducted by Research Seeds revealed that the best recombinant *R. meliloti* strains for alfalfa provide yield advantages over conventional inoculum only in specific soils and when alfalfa has not been grown in previous years (Wacek 1993). It appears the market for the genetically engineered bacteria is more limited than originally believed.

Sandoz officials see the lack of efficacy of *Bt* products, including their own recombinant bioinsecticides, compared to synthetic insecticides as the limiting factor in commercialization and farmer acceptance, not regulatory concerns or public opposition. They have been working to develop recombinant *Bt* strains that will stand up to market scrutiny. Recently, the in-house recombinant virus research program at Sandoz was transferred to another company, Biosys, not because of fears that regulators would disallow field tests but

because of the difficulty of creating an effective microbial product.

### Public Opposition

Following EPA issuance of an Experimental Use Permit to Advance Genetic Sciences in 1986 for field testing the ice-minus bacteria, public opposition to the impending field experiments was organized. Opponents of the tests questioned their safety, emphasizing the unpredictable and possibly catastrophic consequences were the bacteria to escape from the release site (Krimsky 1991). Public suspicion was fueled by AGS's intention to conduct the test without notifying local authorities. The local board of supervisors declared a moratorium on all field tests of transgenic bacteria, which allowed public opposition to stiffen. Subsequently, EPA withdraw the EUP. University of California researchers who, independently, were seeking to field test the ice-minus bacterium at another California location met similar opposition from the local community. After much legal wrangling and negotiating with representative groups, both AGS and the UC researchers succeeded in releasing the genetically altered bacteria in 1987.

In contrast to the strong public reaction to the first environmental releases of GEMs, there has been little attention directed at recent releases. Companies and researchers have also taken a much more proactive stance regarding field releases. Researchers routinely notify local communities about the experiments and provide information regarding the nature of the organisms to be released and safety precautions to be taken. One company found minimal public interest in its open meetings to address public concerns over upcoming field tests. Another researcher typically sends letters to local officials and organizations informing them about field tests so that they can act as a repository of information for the public. In another instance, local volunteers in Massachusetts were recruited to distribute bait containing a genetically engineered vaccine to prevent rabies in raccoons. In 1994, the first test of a recombinant microbe in California, since the ice-minus experience, was carried out with public knowledge and no opposition (Biotech Reporter 1994).

While public controversy over field tests of GEMs has subsided, several of our survey respondents indicated that they were still apprehensive over the possibility their products might be targeted by an opposition group. The controversy surrounding the commercialization of bovine growth hormone by Monsanto was cited in several instances as an indication of the potential problems to which biotechnology was vulnerable. One company official expressed the view that public opposi-

tion had not disappeared but was merely in a dormant state. Another respondent to our survey noted that his company might withdraw its product if it was met with significant public antipathy.

### Conclusions

The early innovators seeking to develop genetically engineered microbes for environmental and agricultural uses considered themselves faced with burdensome and, at times, unclear regulatory requirements. They allocated large percentages of research monies and effort in trying to meeting regulatory requirements. The prospect of field test delays or eventual prohibition of the environmental release and commercialization of GEMs led at least two of these early innovators to discontinue programs and redirect their research efforts elsewhere.

In contrast, researchers and companies requesting clearance to conduct field tests of GEMs more recently have indicated that regulatory requirements are no longer burdensome or unclear. As regulators have gained more experience with GEMs, procedures to obtain clearance for field tests have been clarified and streamlined, and biotechnology companies consider data requirements appropriate for a science-based risk-assessment process. Costs and research effort associated with the regulatory needs have decreased significantly compared to the levels experienced by the early innovators.

Still, a number of R & D programs have been discontinued or have been slow to develop. Our research shows that this has largely been due to the technological difficulty of developing microbial products that can survive and outperform naturally occurring microbes under field conditions. Much of the early euphoria communicated by observers of biotechnology was based on the results of laboratory experiments with GEMs, which appear to have overestimated field performance. The difficulty of establishing introduced organisms in the field, which was known to practitioners of biological control, was not appreciated by molecular biologists. We conclude that the reason most GEM research programs have failed or have been slow to develop was not because of regulatory constraints but because of the failure of the products to provide the intended benefit for which they were created.

A minority of scientists consider the environmental release of GEMs to be essentially risk-free and to be equivalent to the uncontrolled and apparently nonharmful release of microbes that has been carried out widely in agriculture for the last hundred years (e.g., Brill 1991). In our opinion, it would be unwise not to take

seriously the ecological effects of large-scale releases of GEMs and to build a strong science-based ecological risk assessment program to support a regulatory structure. We do not view such a system as inhibiting innovation.

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