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REVIEW

Controlling the Bugs

The First Decade in the Regulation of Biotechnology

RUTH L. GREENSTEIN

Vice President, Genex Corporation, Gaithersburg, Maryland 20877

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ABSTRACT

In late 1984, the Reagan administration proposed a Coordinated Framework for Regulation of Biotechnology. Its proposed regulatory approach appears less constraining than the deep concerns of the 1970s concerning the risk of biotechnology would have suggested. Several distinctive characteristics of the early period of biotechnology, particularly the role of the research community in developing the initial regulatory system and the extent of federal funding, explain this development. The administration's proposal may attract substantial support. However, implementation may lead to conflicts and problems, especially concerning human germ-line gene therapy and environmental release of viable genetically engineered organisms.

Index Entries: Biotechnology, the first decade; biotechnology, regulation of by the administration; research community, role of in regulation of biotechnology; biotechnology and federal funding; human germ-line gene therapy, conflicts and problems of; genetically engineered organisms, release of into environment; biotechnology, regulation of by public.

INTRODUCTION

In the early 1970s, the terms "biotechnology" and "genetic engineering" carried heavy emotional baggage. They conjured up the wonders of science and humanity's ability to control the mysteries of nature. But

they also conjured up the horrors of modern science and our ability to unleash uncontrollable and irreversible natural forces. An analyst then predicting the regulatory future might well have forecast a rigid regulatory system designed especially for the products and processes of biotechnology, a system qualitatively different and administratively separate from these existing for other products and processes.

In December 1984, the Reagan administration published a notice of its *Proposal for a Coordinated Framework for Regulation of Biotechnology.* (*1*) From the perspective of the early 1970s, this proposal is remarkable. First, despite the title, the administration proposed not a uniform national policy, but rather a series of individual agency policies without so much as a uniform set of definitions. Second, the proposal would regulate biotechnology *per se* hardly at all. Instead, with one major exception, the products of biotechnology—the foods, drugs, chemicals, and other products produced by the array of techniques collectively constituting biotechnology—are to be regulated by the same statutory criteria and administrative procedures as their counterparts produced by traditional means. The exception is products involving the environmental release of viable microorganisms.

Public reaction may lead the administration to a more stringent regulatory policy and rigorous implementing regulations. Nevertheless, the notice's apparent lack of concern about biotechnology contrasts so sharply with the apprehension of the mid-1970s as to raise questions about why the policy climate changed. This article first briefly summarizes the administration's proposed framework for the regulation of biotechnology. It then examines some of the characteristics of the early days of biotechnology and some of the events of the decade leading up to the administration proposal. This examination may help explain the outcome. Indeed, it may suggest that the administration's proposed regulatory structure was almost inevitable.

PROPOSAL FOR A COORDINATED FRAMEWORK FOR REGULATION OF BIOTECHNOLOGY

In 1983 and 1984, the administration faced substantial pressure to enunciate a policy on the regulation of biotechnology. The pressure arose in good measure because of impending field testing, or limited environmental release, of genetically engineered organisms. Opponents of these tests sought to block them though litigation. For technical legal reasons, the primary lawsuit (*2*) addressed mainly the narrow issue of whether the National Institutes of Health (NIH) violated the National Environmental Policy Act (NEPA) (*3*) by deleting from its regulatory guidelines (*4*) a prohibition on environmental release without first preparing an Environmental Impact Statement. The litigation increased public awareness of biotechnology; with that awareness came anxiety about unanticipated

outcomes. Although proponents of field testing contended that the microorganism to be released was benign, members of the public wondered whether this organism might not turn out to be as destructive as the gypsy moth or the kudzu vine, the dangers of which had not been fully appreciated at the time of their environmental release. With public concern came congressional concern, hearings, and the possibility of congressional action.

The administration was reluctant to cede control of the issue to Congress. The executive branch is rarely willing to cede anything to Congress, but here there were special reasons for reluctance. The administration believed that regulation of biotechnology was particularly ill-suited to legislative action for at least three reasons. First, the administration believed that the design of a sensible regulatory scheme required an understanding of highly technical scientific questions not likely to be found in Congress. Second, because genetic engineering has the potential to bring about outcomes that raise emotionally charged ethical questions, the administration believed that congressional debate on regulation could easily be diverted to these questions; any resulting legislation might well be undesirable. And third, regulation for reasons of health, safety, and perhaps even morality, needed to be balanced against the need to protect America from losing its lead in this new technology to European or Japanese competitors; the administration thought itself better able to balance these concerns than the Congress.*

Industry supported an executive branch pronouncement on biotechnology (5). With numerous products nearing commercialization, industry feared that continuing regulatory uncertainty and ambiguity would retard innovation. Aware that public concerns had caused substantial difficulties for the nuclear power industry, the biotechnology industry recognized that federal regulation sufficient to calm public fears was perhaps desirable. And industry thought the executive branch less likely than the Congress to embark on wholly new, and therefore unpredictable, regulatory ventures.

Responding to these pressures, the administration acted. In April 1984, it created an Interagency Working Group on Biotechnology under the White House Cabinet Council on Natural Resources and the Environment. The Working Group was charged with: (1) reviewing all laws and regulations applicable, or potentially applicable, to biotechnology; (2) reviewing the role of the NIH Recombinant DNA Advisory Committee

*In the early 1980s, there was widespread fear that the United States was on the threshold of losing its once-commanding lead in microelectronics to the Japanese. In biotechnology, this fear of increasing competition was paralleled by a concern that unduly restrictive or time-consuming regulations would permit the Japanese and the Europeans to reap the commercial benefit of American research and development. For parallels and differences between development of the US semiconductor industry and the development of biotechnology, see US Congress, Office of Technology Assessment, Commercial Biotechnology: An International Analysis, Appendix C, Jan. 1984.

(RAC)* in the regulation and commercialization of biotechnology; (3) determining whether existing statutory authorities and federal review of biotechnology were adequate; and (4) recommending future federal action. Presumably to emphasize the administration's desire to foster, as well as regulate, the emerging industry, the Working Group was further charged with (5) reviewing court decisions on patent protection in the field and (6) reviewing other federal actions involving patents, federal support of research, and other matters affecting the competitiveness of US biotechnology.

The Working Group published its *Proposal for a Coordinated Framework for Regulation of Biotechnology* (*6*) for comment on December 31, 1984.† With two exceptions, the proposal merely groups discrete agency notices conveniently together in one place. The exceptions—a matrix of existing controls and a proposal for a new scientific advisory mechanism cutting across agency responsibilities‡—lend a flavor of cross-cutting coherence, but the proposal in most respects endorses relatively uncoordinated, and therefore potentially inconsistent, agency-by-agency regulation.

The individual agency notices each address basically the same question, although the precise formulation varies according to the agency's underlying statute. If a biotechnologically engineered substance is otherwise identical to a nonbiotechnologically engineered substance previously subject to regulatory action (and, in particular, approval) by the agency, will the agency require special regulatory treatment of the biotechnologically engineered substance? (In the jargon of some regulations, the question is whether a biotechnologically engineered substance is treated as "new" because it is biotechnologically engineered.)

The agencies answered that question in various ways:

(1). The US Department of Agriculture (USDA) said no. Concluding that "no unique or safety problems have been associated with products of genetic engineering, conventional or modern," the department said that it intended to continue with the existing regulatory framework until experience shows it to be inadequate.

(2). The Food and Drug Administration (FDA) answered yes for drugs, but gave no answer for foods and food additives.

*The origins and limitations of RAC are discussed below.

†Federal agencies are generally required by the Administrative Procedure Act (APA), 5 USC § 553 et seq., to provide general notice of proposed rulemaking by publication in the *Federal Register* and to publish the final rule not less than thirty days before its effective date. Agencies may also encourage public participation in policymaking by publishing draft policy statements and soliciting suggestions on particular topics. Publication of the proposal in December was not required by the APA; the proposal solicited public comment.

‡Plans for implementing the new advisory mechanism were not publicly available at the time this article was written. For a discussion of the proposed Biotechnology Science Board, *see Science* **229,** 736 (1985); for a *recent* discussion of its successor, the Biotechnology Science Coordinating Council, *see* Science **230**, 1015 (1985).

Drugs involving recombinant technology are considered new drugs, even if chemically identical to drugs previously approved for marketing. Therefore, all drugs involving recombinant technology are subject to the full premarketing review normally applicable to new drugs. Thus, biotechnologically engineered drugs are treated specially in the determination of new drug status, but not in the regulatory requirements applicable once that determination is made. The FDA made no parallel statement for foods and food additives, but it is not precluded from treating foods and food additives involving recombinant technology as new even if they are otherwise identical to preexisting or approved substances. Most prudent manufacturers will seek FDA approval as if the products are new or ask for an FDA determination that the specific products are not new.

(3). The Environmental Protection Agency (EPA) said yes under two statutes: (a) If a product involving genetically engineered microorganisms, broadly defined is subject to regulation under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (*7*), EPA treats it as new for regulatory purposes. It is therefore subject to premarketing approval; as usual under FIFRA, the applicant must demonstrate product safety. In addition, new genetically engineered products are treated differently from other "new" products in one way. The FIFRA notice reaffirmed EPA's earlier announcement (*8*) that the traditional exemption for research would be narrowed; small scale field testing involving nonindigenous or genetically engineered microorganisms could be done only after due notice to the EPA. (After notice, the applicant may proceed unless informed by the EPA that the agency wants an Experimental Use Permit.) Environmental release of genetically engineered organisms is thus specially treated. (b) If a product involving genetically engineered microorganisms, narrowly defined, is subject to regulation under the Toxic Substances Control Act (TSCA) (*9*), EPA considers it "new" for regulatory purposes.* Because new and, therefore, not on the TSCA Chemical Substance Inventory (inventory), it is

*In the section of the *Register* notice dealing with FIFRA, EPA's Office of Pesticide Programs defined genetic engineering to "include more than [organisms] modified by rDNA techniques. Therefore, microorganisms modified by rDNA techniques as well as by cell fusion, conjugation, microencapsulation, microinjection, directed or undirected mutagenesis, plasmid transfer, trasformation, and so on, are included." **49** Fed. Reg. 50,884. The EPA's Office of Toxic Substances, in contrast, has defined as new only those microorganisms produced by rDNA, rRNA, and cell fusion techniques and simply solicited comments on the appropriate treatment of the products of all of the other techniques included in the FIFRA portion of the notice. Id. at 50,887–8.

> subject to premarketing notification with, as is usual under TSCA, the burden on the government to show that the product presents an unreasonable risk to health or the environment. Although the facts and information necessary to support an application for approval of a genetically engineered microorganism will be different from those required for standard chemicals, regulatory treatment of new genetically engineered products is essentially identical to the regulatory treatment of other "new" products. However, EPA left open the possibility of narrowing the traditional research and development (R&D) exemption, so that, as with FIFRA, biotechnology research may become subject to greater federal scrutiny than R&D in general.

Whether or not the proposal represents a "business as usual" approach to regulation, it clearly does not recommend the kind of strict control of biotechnology that might have been predicted a decade earlier. To understand why requires looking at the situation in the mid-1970s and events that followed.

EVOLUTION: FROM THE BEGINNINGS OF REGULATION IN THE EARLY 1970S TO THE PROPOSAL

The 1984 administration proposal concerning biotechnology reflects the regulatory institutions and debates of the 1970s, which themselves were influenced by the three characteristics of the early history of biotechnology. First, in the early days of biotechnology, the research scientists themselves were at the forefront of the call for controls. Second, the research was almost entirely conducted on university campuses, which permitted the development of a relatively informal and flexible system of controls implemented through conditions on federal funding of research instead of traditional formal regulation. And third, the early regulatory framework developed when rDNA technology was almost entirely research oriented, so that issues such as field testing, product safety, and international competitiveness could be deferred.

Scientific Involvement

The first calls for regulation of biotechnology came not from traditional political entrepreneurs, but rather from the very scientists who were doing research on recombinant DNA. These scientists called for regulation not to forestall others from controlling the issue, but out of deep concern that the technology posed serious risk to laboratory workers and the public. They approached the task of designing a regulatory framework not, as is often the case when an industry seeks to be regulated, to prevent others from creating a more inhibiting regulatory structure, but rather with the sincere desire to design a system that responded

to perceived risks. Thus, the regulations were designed by the regulated, based on their scientific judgments at the time and were changed over time as these judgments were modified. An understanding of the origins and evolution of scientists' concerns about the dangers of recombinant technology is therefore necessary to an understanding of the change in regulatory approach.

Scientific concern about recombinant DNA technology arose early in the history of biotechnology. Individual scientists voluntarily refrained from certain experiments in the early 1970s. The attendees at the prestigious 1973 Gordon Conference, which that year focused on nucleic acids, urged the National Academy of Sciences (NAS) to establish a study committee to consider the problem and make appropriate recommendations (*10*). The NAS's initial committee formed by the academy made several recommendations in July 1974: First, that scientists defer certain experiments for the time being; second, that NIH establish an advisory committee to evaluate the biological and ecological hazards of recombinant DNA and to devise research guidelines; and third, that an international meeting of concerned scientists be convened to study the problem further (*11*). In October 1974, the director of NIH established the NIH/RAC, charged as a technical committee

> to investigate the current state of knowledge and technology regarding DNA recombinants . . . ; to recommend guidelines for the conduct of DNA experiments; and to recommend programs to assess the possibility of spread of specific DNA recombinants and the possible hazards to public health and the environment (*12*).

In February 1975, the NAS, along with the NIH and the National Science Foundation (NSF), sponsored the Asilomar Conference on Recombinant DNA Molecules.

The report of the Asilomar conference, attended primarily by scientists, was a seminal document in the development of the regulation of biotechnology, laying much of the foundation for what happened in the years after. It made three critical recommendations (*13*). First, it recommended that "most of the work on construction of recombinant DNA molecules should proceed provided that appropriate safeguards . . . are employed." Second, it concluded that adequate containment, both physical and biological, must be considered an essential feature of each particular experimental protocol. The concept of biological containment was quite novel at the time. Third, it concluded that certain experiments "present such serious dangers that their performance should not be undertaken at this time with the current vector–host systems and the presently available containment capability." Included in Asilomar's list of prohibited experiments (experiments to be deferred) were cloning of recombinant DNA from highly pathogenic organisms (i.e., CDC class 3, 4, or 5 etiologic agents); experiments involving DNA containing toxin genes; and experiments involving over 10 L of culture, using recombinant DNA capable of making products potentially harmful to man, animals, or plants.

The first NIH/RAC meeting, held right after the Asilomar conference, proposed that the Asilomar recommendations be adopted as interim guidelines for research until more specific guidelines could be worked out (*14*). The RAC itself started to draft guidelines during the summer of 1975; in mid-1976 it issued the NIH Guidelines for Recombinant DNA Research (*15*).

Original NIH Guidelines

Like the Asilomar Guidelines, the 1976 NIH Guidelines reflected the scientists' continuing concern about the potential danger of the new technology. Because of concern that the Asilomar Guidelines were not strict enough, NIH decided to issue its original Guidelines before completing the environmental impact assessment required by NEPA. As the notice in the *Federal Register* said, "because the NIH Guidelines will afford a greater degree of scrutiny and protection [than the Asilomar Guidelines], they are being released today and will be effective while the environmental impact assessment is under way." (*16*)

The basic premises of the NIH Guidelines were almost identical to those of the Asilomar Guidelines, namely, that most experiments could go forward with appropriate physical and biological containment—but that there were certain experiments for which the assessed potential hazard was so serious that they could not be attempted at that time. The Guidelines listed six prohibited experiments (experiments not to be performed). The list included, in addition to those of the Asilomar Guidelines, prohibitions on: (1) the deliberate creation from plant pathogens of recombinant DNA likely to increase virulence and host range; (2) the transfer of a drug resistance trait to microorganisms that do not normally acquire it if that would affect pharmaceutical effectiveness; and (3) the "deliberate release into the environment of any organism containing a recombinant DNA molecule." (*17*)

The flat prohibition on deliberate release led to the litigation mentioned above. The NIH adopted it, despite the recommendation of at least one member of RAC that environmental release be permitted once certain tests had been performed. It did so because of the NIH director's judgment that the scientific evidence to justify such release did not exist at that time. Because environmental release was prohibited, NIH's Environmental Impact Statement, prepared in conjunction with the original Guidelines, devoted little analysis to the risks of such release. Nevertheless, the prohibition can be read as an agency conclusion that the potential risks were disproportionate to the possible benefit.

NIH Guideline Revisions

The NIH Guidelines changed considerably between 1976 and 1984.*

*So did the process for modifying the Guidelines. The revised 1978 Guidelines substantially increased public participation in the decision-making process. Moreover, they provided that important decisions to approve otherwise prohibited experiments on a case-by-case basis or to change the Guidelines required public notice and comment.

The successive modifications of the Guidelines probably provide the best available insight into changing scientific attitudes toward the dangers of biotechnology and consequently into the attitudes that underlie the proposed regulatory framework now under review. For present purposes, it is sufficient to compare the Guidelines at two points, 1976 and 1984.

Perhaps the most striking difference between the 1976 and 1984 Guidelines (*18*) concerns the role of the federal government. Under the 1976 Guidelines, NIH and RAC had to review and approve all recombinant DNA experiments (other than those expressly prohibited under any and all circumstances). Although the 1976 Guidelines mandated creation of an Institutional Biosafety Committee (IBC) at each institution undertaking DNA research to advise the institution on policies and certify compliance with certain aspects of the Guidelines, decision-making authority lay in Washington. By 1984, federal oversight had in large measure been supplanted by the judgment of each research institution's own IBC. The system had evolved from one of centralized federal oversight, with substantial advice from the regulated in the form of RAC recommendations, to one of decentralized self-regulation by the regulated, based on published NIH rules and regulations. Other industries undoubtedly envy this evolution toward self-regulation.

Substance as well as process has changed over the years. The 1976 list of prohibited experiments was sweeping. A decade later, almost nothing is prohibited. Three of the original six prohibited experiments are now permitted, subject to prior review, most, but not all, of the time, by NIH/RAC. Thus, for example, research involving the deliberate formation of recombinant DNA-containing genes for the biosynthesis of potent toxins requires NIH review, unless the LD_{50} is 100 or more ng/kg of body weight, in which case IBC review is sufficient (*19*). The 1976 prohibition on experiments involving the transfer of a drug resistance trait to microorganisms that are not known to acquire it naturally, if that would compromise the use of a drug to control disease in humans, animals, or agriculture, has similarly been converted into a requirement for prior NIH/RAC approval (*20*). And the deliberate release into the environment of microorganisms containing rDNA is now permitted by the Guidelines once prior NIH approval has been received (*21*).

Some of the original prohibitions have been downgraded even further. In 1976, research involving any substance classified by the CDC as a class 3, 4, or 5 etiologic agent was prohibited entirely. In 1984, most of these same experiments require only prior IBC approval (*22*). Similarly, experiments involving over 10 L of culture are basically governed by the judgment of the IBC rather than of the RAC and the NIH (*23*). As the years progressed, requirements for extraordinary physical containment were also reduced, as fears of unintended consequences declined.

The most striking substantive change may be that many rDNA experiments are now exempt entirely from the Guidelines because of a judgment that they do not pose any risk either to the researchers or the

population at large. Thus, most experiments involving *Escherichia coli* K-12, *Saccharomyces cerevisiae*, and sporulation-deficient strains of *Bacillus subtilis* are now exempt entirely from the Guidelines (*24*). Most experiments involving organisms that exchange DNA in nature are also exempt, even if potentially hazardous—presumably on the theory that humans should be allowed to make the same mistakes as Mother Nature. As a result, much, perhaps most, of the research now being conducted using recombinant DNA techniques may be initiated prior to any regulatory review. If a researcher decides that his or her project is NIH-exempt or requires only simultaneous notification to the local IBC, the researcher can go forward immediately and submit relatively limited documentation to the IBC for after-the-fact confirmation. The contrast with the lengthy rules regarding *E. coli* K-12 in the original Guidelines is striking.

To the extent that the NIH Guidelines reflect the judgement of the scientific community, the changes since 1976 suggest continually diminishing scientific concern about the dangers of genetic engineering. Because the scientific community includes scientists in government who where influential in creation of the December 1984 proposal, it is no surprise that this relative lack of concern is mirrored in the regulatory system proposed. Perhaps the starkest statement of the regulators' lack of concern about biotechnology, as such, came in an April 1985 *Federal Register* notice from the Occupational Safety and Health Administration (OSHA). In that notice, OSHA explained its decision against additional regulation of workplaces using biotechnology: "No hazards from biotechnology *per se* have been identified." (*25*)

Campus-Based vs Industry Research

The institutional location of early biotechnology research had a profound effect on the legal structure of the regulatory mechanism and the ability of that mechanism to respond quickly to changing scientific views.

Early rDNA research was almost entirely campus-based. Since the 1960s, campus-based research in this country has been heavily federally funded. In 1981, for example, some two-thirds of all research in science and engineering performed in American colleges and universities was funded by the US government (*26*). Privately funded research is frequently conducted at institutions receiving federal money; the proportion of campus science and engineering research conducted at institutions receiving federal money probably exceeds 90%. All research at such institutions is amenable to control through conditions on funding. As a result, the NIH Guidelines, originally applicable only to NIH grantees, but soon extended by other agencies to their own contractors and grantees, managed to regulate most biotechnology research even though they were only voluntary at any institution not receiving federal money.

Regulation by imposition of preconditions to the receipt of federal funding facilitated the regulatory process by eliminating entire categories

of potential disputes. Because few question that a research sponsor can set the terms and conditions under which it will award money, the legitimacy of regulation, as such, was not generally questioned. Moreover, it is widely believed that the government may sometimes control by contract that which it may not constitutionally control by ordinary regulation (*27*), so the incorporation of the Guidelines into federal contracts and grants avoided tortuous constitutional debate and, perhaps, lengthy litigation.

Control by precondition to funding was important for another reason as well. It encouraged a relatively informal, responsive system capable of adapting to changed circumstances and evolving scientific views in a fashion that would be difficult in the case of more formal regulation.

The initial regulatory apparatus could not serve as the long-term mechanism for controlling the new technology because it depended on the federal government's having a lever in the form of funding controls. If the technology were ever to leave the laboratory for the marketplace, industry would become involved, and industry would generally not be subject to these funding controls. Indeed, it was not long before industry became active in rDNA research as firms developed their own research capabilities—sometimes by simply hiring the academics—and as academic researchers themselves created small companies and other business enterprises. Not unexpectedly, industrial involvement intensified as the prospect of profits arose.*

In 1977, the Federal Interagency Advisory Committee on Recombinant DNA Research recommended national legislation to make the Guidelines binding on industry, but the legislation bogged down in Congress. The NIH then tried to address the situation through the Guidelines by urging "individuals, corporations, and institutions not otherwise covered by the Guidelines . . . to follow the standards and procedures of the Guidelines." (*28*) Without legislation to transform the Guidelines into full-fledged regulations with the force of law, NIH could only urge, not require. Industry—sensitized by the problems of the nuclear industry to the need for public support and generally assuming that the Guidelines would be considered the applicable standard of care in any tort litigation—generally did comply. But at the time, compliance was cheap, and there was a nagging doubt about what would happen if RAC and NIH turned down an industrial project that a particular company thought likely to be highly profitable.

Some localities were not convinced that industry would continue to comply in that situation. One result was a spate of local legislation, mainly in localities such as Boston, Cambridge, and Berkeley, with both

*Although many other factors were involved, the 1980 Supreme Court decision in Diamond vs Chakrabarty, 447 US 303, holding life forms patentable subject matter substantially increased industry's ability to protect this form of intellectual property and, thus, its interest in investing in biotechnology.

major research universities and spin-off biotechnology companies. By and large, these ordinances simply required private companies to adhere to NIH Guidelines. Some, however, were more stringent; some became more stringent because they incorporated a specific version of NIH Guidelines and did not incorporate amendments to the Guidelines relaxing the rules. The specter of diverse local regulation appears to have helped convince industry that federal regulation might not be such a bad thing—particularly given the federal government's demonstrated willingness to allow the scientists to play a major role in designing the outcome.

In sum, the campus location of almost all early DNA research permitted a flexible, at times informal, approach to regulation at a time when fears about the new technology were at their peak. But because not-for-profit research universities were unlikely to be the instruments of commercialization, that early system was clearly destined to be overtaken as industry's role increased.

Laboratory vs Market Orientation

The advent of commercializable products created new problems for the flexible and informal regulatory approach that had thrived when no commercial products were on the short-term horizon. First, the stakes became higher, making it more likely that industry would bolt if NIH/RAC recommended against doing something industry really wanted to do. Second, and perhaps more important, it was not clear whether NIH was the right institution to regulate commercial biotechnology.

The NIH and its RAC were both expert and respected as overseers of laboratory-based medical research; they were not constituted to regulate commercial activities and lacked both the expertise to deal with the environmental issues associated with intentional release and the inclination to be a regulatory body in the traditional mold. Even with the addition of representatives of additional disciplines and the public interest, RAC expertise in environmental issues is still very much subject to challenge. The NIH and RAC were clearly not the right forum to deal with the ethical and cultural problems of genetic engineering. The RAC was expressly chartered to be a technical committee to look at specific problems. Neither the NIH nor the RAC had the expertise or a mandate to worry about the even broader questions of international competitiveness or of threats to US national security from certain applications of biotechnology. Indeed, some have argued that NIH's dual capacity—as both a principal proponent of further biomedical research using biotechnology and a regulator—creates a conflict of interest for that agency.

The increasing inappropriateness of NIH as the government-wide regulator of biotechnology almost inevitably led to a series of agency-by-agency pronouncements as individual agencies saw the new technology applied in areas under their ordinary regulatory jurisdiction. Beginning

with the FDA's Notice of Intent to Propose Regulations, each of the agencies with some responsibility for product clearance, health, safety, and the environment began to look to its underlying statute and implementing regulations to see how they could be interpreted, stretched, or modified to reach the new technology. No existing regulatory agency combined the interest, the capability, and the legal authority to address regulation of biotechnology across the board.

A GUESS ABOUT THE FUTURE

Whether the regulatory framework proposed last December will prove viable is an open question. The full implications of the framework depend on regulatory details still to be devised. Perhaps more importantly, both environmental release and human gene therapy raise ethical, legal, and emotional disputes difficult to manage within any regulatory framework.

Specifying the Details

The administration's proposal is only a beginning. General statements must be translated into specific regulatory language. Translation is likely to be slow and difficult. The wording of proposed regulations matters considerably to the potentially regulated; minor changes can mean the difference between being regulated and not being regulated, between having an easy case to prove and having an almost impossible one. These changes may involve complex technical decisions. The Chemical Substance Inventory (inventory) maintained by the EPA under TSCA provides a good example. If a particular substance is listed on the inventory, no premarket notification (PMN) is required. If the substance is not listed on the inventory, a manufacturer must submit a PMN to the EPA and wait six months, a year, or more before it can sell the product.

How substances are listed has profound implications. The method for listing traditional chemicals on the inventory is well known; that for listing genetically engineered organisms has yet to be decided. To illustrate how differently the same substance can be listed, the EPA has provided alternative inventory entries for a pig gene for pancreatic serine proteinase inserted into the chromosome of *E. coli* (*29*). At one extreme, it could be listed simply as *E. coli* porcine proteinase. This formulation would cover any strain of *E. coli*, any location of the gene, and any type of proteinase; PMNs would be required infrequently. At the other extreme, the listing could also designate the strain, the method used to produce the new organism, or the nucleic acid of the inserted DNA. This approach would require a PMN for every significant modification of the organism. Which approach makes scientific—and administrative sense—is not yet clear, but the choices matter to the regulated.

Managing Disputes

Although specifying details will be difficult, the government, industry, and public are likely to reach some working consensus. On the other hand, application of those regulations to highly charged questions of environmental release and human gene therapy may not result in a working consensus. The regulatory system may prove unable to reach workable and generally accepted decisions in an efficient and timely manner.

Environmental Release

Much of the current public concern about biotechnology focuses on the possible dangers from the environmental release of genetically engineered microorganisms. Where issues of environmental release arise, any regulatory system may have difficulty.

The regulatory history of experiments proposed by S. Lindow and N. Panopoulos may suggest the course of things to come, although unusual issues may have been involved. In September 1982, Lindow and Panopoulos, professors at the University of California, Berkeley, requested NIH approval to field test ice-nucleation-minus bacteria prepared by recombinant DNA techniques. The NIH/RAC recommended approval of the experiment by a vote of seven to five, with two abstentions. The NIH withheld approval. In March 1983, Lindow and Panopoulos submitted a revised proposal. The RAC voted to recommend approval of the project subject to certain modifications. On June 1, 1983, NIH announced that it had approved the experiment (*30*). In September, the Foundation on Economic Trends, headed by Jeremy Rifkin, sued to block the experiment (*31*) . In May 1984, the US District Court for the District of Columbia enjoined NIH approval of any deliberate environmental release and enjoined the University of California from proceeding with the Lindow–Panopoulos experiment (*32*). In February 1985, the US Court of Appeals for the DC Circuit vacated the injunction as it applied to future approvals of deliberate release experiments by the NIH, but upheld the injunction as it applied to the University of California, pending the completion of an environmental assessment (*33*). The NIH completed the environmental assessment in January 1985 and in April announced the Assessment's Finding of no Significant Impact and its availability for notice and comment (*34*). By July 1985, when this article was prepared, NIH had gotten no further than to announce the availability of its analysis of the public comments (*35*).

Experiments like the Lindow–Panopolous experiment may also be subject to regulation under FIFRA. In October 1984, EPA published its Interim Policy on Small Scale Field Testing of Microbial Pesticides (*36*), which appeared to provide for relatively easy approval of such experiments through notice and failure of the EPA to disapprove. Advanced Genetics Sciences, Inc., which was working in collaboration with the University of California on the Lindow–Panopoulos experiments and

whose voluntary request for NIH approval was bogged down in the same morass, withdrew its request to NIH in February 1985 and submitted the required notice to EPA instead. (The University of California, because it received federal funds, required both NIH approval and EPA clearance.)

The EPA, however, is subject to similar pressures, and has been slow to permit environmental release. By early summer 1985, it had received four notifications under the Interim Policy. Three—including one from the University of California and another from Advanced Genetic Sciences, Inc.—involved the release of viable microorganisms; one involved the release of dead microorganisms. The latter was permitted to proceed. For the three proposals involving viable organisms, however, EPA required the submitter to request a full-scale Experimental Use Permit. This delayed the time of decision—no final decision has yet been reached*—and increased the cost of regulation. The EPA's decision to require the further submission may simply reflect the inadequacy of the notices originally submitted. However, EPA surely recognized that approval of the experiments could cause substantial political furor.

At least implicitly, any approval or disapproval addresses whether the risks of environmental release outweigh its potential benefits. Given the charged atmosphere surrounding this issue and its broad implications, and the relatively narrow focus of regulatory decisions on particular experiments, the regulatory structure has difficulty making these decisions.

Gene Therapy

Similar, but more extreme, problems arise in regulation of human gene therapy. In theory, the regulatory system already in place at NIH and FDA should apply to human gene therapy with little modification. Most medical researchers already comply with the NIH Guidelines; any new drug produced will be subject to FDA review and approval. In practice, however, alteration of the genome of human cells, even more than the release of genetically engineered organisms, is likely to raise exceedingly contentious and emotional issues. The debate is likely to come in stages, focusing first on somatic gene therapy (in which the objective is to correct a specific noninherited genetic defect) and only later on germ-line gene therapy (in which the objective is to modify inherited characteristics). Because the former involves only the immediate patient, reaching agreement on the terms and conditions under which somatic gene therapy may proceed should be relatively simple compared to reaching agreement on when germ-line gene therapy should be permitted.

Somatic gene therapy raises traditional questions almost identical to those raised by any new drug or other experimental medical therapy (*37*). Is the procedure safe and effective? Is the patient fully aware of the

*Since this article was submitted, EPA has approved field tests of genetically engineered organisms by Agracetus and by Advanced Genetic Sciences. *See Science* **230**, 1015 (1985).

risks involved? Are there alternative procedures that might be preferable? But it may also raise far-reaching social issues.

The scope of the issues raised is indicated in NIH's proposed *Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols* (*38*). The bulk of this publication focuses on the traditional technical information necessary to make decisions about the scientific merit and safety of the protocol. But part II of this *Points to Consider* explicitly focuses on social issues. It indicates that RAC, in considering any proposal for somatic-cell gene therapy, will consider not only the likelihood that the proposed somatic-cell gene therapy will, in fact, affect the reproductive cells, but also whether "it is likely that somatic-cell therapy for human genetic disease will lead to (a) germ-line gene therapy, (b) the enhancement of human capabilities through genetic means, or (c) eugenic programs encouraged or even mandated by governments." (*39*) How RAC and the NIH will answer the last set of questions remains to be seen. What they will do with the answers is still less clear. How these agencies are to balance scientific merit against the prospect of mandated eugenics is a mystery. The prospect that the society at large will leave this balancing to a relatively obscure governmental agency and its still more obsecure advisory committee is dubious.

As these NIH *Points to Consider* suggest, enormous hostility to germ-line gene therapy exists. Indeed, there is a *de facto* moratorium on research on such therapy at this time. Germ-line gene therapy raises religious and ethical issues. There are also more practical questions about the likelihood of long-term unpredictable effects and the possibility and consequences of diminishing human genetic diversity (*40*). Finally, there are legal issues concerning the government's power to restrict research for reasons of morality rather than of health, safety, or national security.*

These issues are ill-suited to traditional benefit–risk analysis. The questions are not purely technical, the tenor of the debate not likely to be dispassionate. Procrastination as a policy may be wise for the moment, but society will eventually have to decide whether and when gene therapy will go forward. The administration's December 1984 proposal may have created a viable framework for regulating the marketing of, say, genetically engineered chemicals or pharmaceuticals. The likelihood that it created a viable framework for regulating human germ-line gene therapy is lower.

*Some commentators argue that the conduct of scientific research is protected by the free speech clause of the First Amendment to the US Constitution. See J. Ferguson, Scientific Inquiry and the First Amendment, **64** Cornell L. Rev. 639, 640–48 (1979). If such a view prevailed, governmental restrictions on research would be judged by the demanding criteria applied to protect freedom of speech. Under these criteria, regulation rationalized primarily by moral concerns would likely be found unconstitutional.

CONCLUSION

The regulatory approach to biotechnology that evolved during the 1970s and early 1980s benefitted enormously from the fact that the regulators, primarily NIH and RAC, developed a system that both encouraged public participation and made decisions incrementally as the state of scientific knowledge advanced. Because the art was still young, the regulators could avoid many of the thorny issues that required knowledge then beyond the horizon. But what was almost inconceivable a decade ago may be merely impractical today and on the agenda for tomorrow. Thus, many issues can no longer be deferred or couched in purely technical terms. Fundamental value judgments will have to be made affirmatively or by default.

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