BIOTECHNOLOGY AT THE CROSSROADS
IS REGULATION THE GATEKEEPER?

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As of May 1991, the United States Department of Agriculture (USDA) had approved approximately 120 applications for small-scale field trials of transgenic plants and several genetically engineered animal biologies had been approved for marketing. The Food and Drug Administration (FDA) had approved for commercial use one biotechnologically derived food enzyme and the Environmental Protection Agency (EPA) had allowed a handful of genetically engineered pesticides and other organisms to be used in the field and in closed systems. As the science of molecular biology appear to progress, quickly bringing agricultural applications of biotechnology closer to the marketplace, we, the organizers of this third NABC meeting, thought the time appropriate to focus our discussions on biological, social and institutional questions voiced about biotechnology and how concerns might affect the pace of development and commercialization of agricultural biotechnology.

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My task today is to review the regulatory structure for the agricultural products of biotechnology. After a brief introduction, where I adopt the viewpoint that agricultural biotechnology is at "a crossroad," I will present, in an historical context, an overview of the current regulatory system and conclude with an evaluation of the effect of the regulatory framework on the pace of commercialization. My conclusion is that consumer acceptance and scientific problems, as well as problems in the regulatory system, will continue to slow the pace of approval of the products of agricultural biotechnology.

IS AGRICULTURAL BIOTECHNOLOGY AT A CROSSROADS?

There is little doubt that agriculture has been, and regardless of the pace of regulatory approvals, will continue to be greatly affected by biotechnology. New crops are being developed, as are new animal drugs and vaccines, and there is an explosion of understanding about the basic biology in agricultural systems. Today there are several new agricultural biotechnology companies and most of the large traditional players in the agricultural sector—seed companies, pesticide companies, livestock producers and food processors—have biotechnology initiatives. Therefore, from a long-term perspective, agriculture and biotechnology appear as healthy partners.

From a short-term commercial perspective, however, agricultural applications of biotechnology appear to be at a crossroads. There are many strong supporters for the majority of agricultural applications of biotechnology in agriculture. However, unlike their biomedical cousins, which have been viewed from the outset as valuable and have been commercialized almost without controversy, questions have been raised by some from the very beginning about the need for, and the social, political, economic and safety implications of initial targets for commercialization of biotechnology in agriculture. Wide-ranging public debate has taken place long before any products have entered the commercial arena. Focusing not just on the traditional concerns of environmental and human safety, but on new criteria such as potential economic, social and philosophical issues, the debate has made the process of formulating a rational regulatory scheme more uncertain and protracted. Coupled with a shortage of agency resources, the pace of agency consideration and development of policies toward products of biotechnology used in agriculture has been slow and the resulting uncertainty and cost has caused a number of the smaller companies to depart from the industry as well as a reduction in the efforts of some larger companies.

Therefore there is a "crossroad"—the smaller companies may not have the wherewithal to last through the continuing debate and regulatory uncertainty. In my view, the question is not whether biotechnology will be commercialized in agriculture, but when and by whom. Of the four determinants—science, intellectual property, regulations and acceptance by

consumers, farmers and processors—I will be focusing on the latter two. The question I ask at this point is, "Have we created a system in which only the biggest or largest can survive?"

OVERVIEW OF THE REGULATORY FRAMEWORK

In June 1986, the President's Office of Science Technology Policy (OSTP) published the Coordinated Framework for the Regulation of Biotechnology (51 *Federal Register,* 23302 *et seq.,* June 26,1986). In 1987, USDA published a revision to the 1986 proposal, (52 *Federal Register* 22892, June 16, 1987). These documents contain the basic framework for the regulatory oversight of the products of biotechnology. The development of the framework can be traced back to the 1970s.

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HISTORICAL LESSONS

The history of recombinant DNA regulation, a period of only 15 years, is instructive for the current debate. The history can be viewed in three parts. The first period, ending in about 1978, was characterized by conjectural fears about laboratory-based research, raised initially by the scientific practitioners and then spread into the political and public arena. Notwithstanding numerous Congressional hearings and media attention, the issues were largely laid to rest as a result of the adoption of "guidelines" issued by the National Institutes of Health (NIH). The NIH Guidelines set the standard and today, as laboratory experience has allowed relaxation of the Guidelines, 90 percent of laboratory research is exempt from the Guidelines.

Some observations about this period are instructive when contrasted to the current debate. One, a scientific and political consensus was developed within a relatively short period of time, approximately three years. The NIH played a major role, together with the scientific community, in helping to allay public fears and put in place flexible, yet credible, guidelines. Two, the regulations were entirely process-based; that is, the regulations focused entirely on recombinant DNA molecules; there was no efforts to recast all regulatory authorities to the new science. Three, the Guidelines focus on lab experimentation, primarily in the biomedical field; environmental releases were generally prohibited.

The second period of the regulation, or oversight of recombinant DNA technology, begins in the early 1980s and was highlighted by the commercialization of the initial biomedical applications of the technology and the development of potential agricultural and environmental applications of biotechnology. The biomedical field turned out to be largely non-controversial; agricultural applications sparked a significant debate which is ongoing.

Two observations seem appropriate. First, because the initial biomedical products were viewed as potentially lifesaving or dealing with serious diseases, none raised significant public policy questions. Second, the products were the providence of one agency—FDA—and traditional concerns were focused on in the FDA regulatory structure, e.g., safety and efficacy[1].

In contrast, agricultural and environmental biotechnology products were viewed as presenting a very different perspective because living organisms were to be introduced into the environment or intended for human consumption. Started by a series of congressional hearings before the Oversight Subcommittee of the House Science and Technology Committee, and continued with a review by the White House, the new applications of biotechnology were examined to determine whether the current laws and regulations were adequate to protect the public while not unduly impeding the technology. It is this debate that is still going on, now almost a decade later.

As before, several observations seem useful. First, the focus of the debate shifted from laboratory experiments by academic researchers and development of lifesaving medicines, to planned introduction by companies into the environment of genetically modified plants, animals and microbes and to introduction into the food chain of food products from these organisms. Second, because of the wide ranging potential uses of these new products several agencies were now involved, frequently in areas where they either had not previously regulated or in overlapping areas. In addition to FDA, agricultural applications involve principally EPA and USDA. As a result, there have been and continue to be, disagreements

[1]While FDA has had to address many issues involved in evaluating new biotechnology products, the issues have been mostly traditional concerns in the drug approval process.

about the scope of the organisms reviewed, agency jurisdiction and risks and benefits of specific applications.

The third period of regulatory oversight of biotechnology begins with the publication of the Framework in 1986 and continues into the present. During this period the agencies reviewed various applications involving mostly small scale field trials. While unsuccessful, there were also many EPA efforts to modify the Framework in light of increasing experience and efforts by USDA to develop guidance for large scale testing and commercialization of biotechnology products.

The Framework addresses the jurisdictional basis of the regulation of the products of biotechnology; it describes EPA's, USDA's and FDA's jurisdiction, together with that of NIH and the Occupational Safety and Health Administration. The Framework is grounded in four principles. The first is that existing statues are sufficient; *e.g.,* no new laws are necessary. The second principle is that the product, and not the process used to develop the product, would be the regulatory focus—the basis of regulation would be the end product and not how that product was produced. The third is that regulation would proceed on a case-by-case basis, and not by class, until there was sufficient information to make determinations about the safety or lack of safety of classes of products. The fourth principle is that the agencies would attempt to coordinate and to work reviews in conjunction with one another, rather than sequentially.

The Framework principally focuses on small-scale introductions and, while describing in some detail agency programs for approval of traditional products, it provides little guidance on large scale and commercial issues. Several applications, for example, transgenic animals, are not discussed, nor are regulatory questions with respect to commercialization of products of transgenic plants, the registration of pesticides or herbicide-tolerant crops Notwithstanding its deficiencies, the agencies and particularly USDA, have used the Framework as a mechanism to allow some research applications to move into the field trial stage.

A brief description of each agency's regulatory program follows.

USDA—The Animal, Plant Health and Inspection Service (APHIS), relying on the Federal Plant Pest Act (7 U.S.C. §§ 150aa-150jj) requires that a permit application be filed before movement, defined to include an environmental introduction, of any organism produced via genetic engineering

which has a plant pest source (donor, vector or recipient) and any organism having a potential plant pest risk. Principal concerns of APHIS have been the source of the organism and its ability to present a risk to agriculture. The agency has also used its authority under the National Environmental Policy Act (42 U.S.C. §§ 4321-4370) to conduct environmental assessments.

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To date, APHIS has granted approximately 1,000 permits for movement of genetically engineered organisms for lab research and approximately 120 permits for actual field trials. Of the field trial permits, about 40 percent have involved herbicide tolerant plants, with the balance for pest and viral resistance and some few for plants with compositional modifications. In addition to tobacco and tomatoes, the initial targets, many vegetable and some tree and fruit crops, have been tested in the field.

Under the authority of the Virus, Serum and Toxin Act (21 U.S.C. §§ 151-158) APHIS regulates production and sale of animal biologies, such as animal vaccines and some diagnostic tests used in the treatment, prevention, cure and diagnosis of diseases of animals. APHIS has approved three licenses for a recombinant vaccine and approved field testing of another vaccine. The basic questions asked by APHIS in the review are traditional to agency concerns: potency, purity, efficacy and safety. APHIS also evaluates environmental considerations and on one such occasion, environmental issues have held up a permit approval.

Most observers believe that APHIS's program for review and permitting small scale trials of plants has been successful; APHIS has allowed for public and state participation and has conducted credible reviews on a timely basis. APHIS also has sought to stimulate thinking about downstream considerations by sponsorship of conferences, such as the meeting on transgenic maize held at the Keystone Center.

EPA—EPA's biotechnology policy relies on its authority under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) (7 U.S.C. §§ 136-i36y) and the Toxic Substances Control Act (TSCA) (15 U.S.C. §§ 2601-2629), to regulate pesticides and chemicals respectively.

Chemicals, which EPA has defined to include DNA, are subject to a 90-day premanufacture notification requirement, if they are not on EPA's inventory of existing chemicals in commerce. EPA's review has focused on enhancement of the host range of the modified organism and the ability of

the organism to affect the ecosystem and human health. EPA has received notification for small-scale field testing of microbes used for nitrogen fixation and for several genetically modified microorganisms used in closed systems to produce enzymes for non-FDA regulated uses. (The enzyme itself is treated as traditional chemicals for regulatory purposes.) Taxonomy has been a major issue for EPA as well as definitions for the scope of organisms subject to review.

Under its FIFRA policy EPA focuses on the small scale field testing of biological pest control agents. EPA adopted a policy of requiring agency notification prior to any field testing of certain genetically modified organisms. EPA has received several notifications, and most small-scale trials have proceeded without the need for an experimental use permit. (Field tests of chemical pesticides on less than ten acres remain exempt from notification and experimental use permit requirements.)

EPA has not been successful in modifying its 1986 policy statement notwithstanding several efforts that have come to the proposal stage. Disagreements about the scope of organisms subject to notification and regulation, as well as agency turf battling, have led to this stalemate, but many are hopeful that the current proposed revisions will be published and the public debate will begin. Not addressed in the revisions, and still to be decided are the downstream issues: how to regulate, if at all, plants with increased pesticidal properties, whether to regulate herbicide tolerant crops, and how to address the tolerance/residue issues.

FDA—FDA regulates in several areas which affect the agricultural applications of biotechnology including food and animal feed, food additives, animal drugs and possibly transgenic animals. FDA's basic authority is the Federal Food Drug and Cosmetic Act (FFDC Act) (21 U.S.C. §§ 301-392). While FDA has approved several genetically engineered foods, animal biological for human use, no genetically engineered foods, animal drugs or feed additives have been approved as yet. One food enzyme has been approved.

FDA has not generally provided guidance as to how it will regulate the products of biotechnology, though it has stated on more than one occasion that it will rely on its traditional programs. FDA does not regulate foods on a pre-market clearance basis. Traditionally bred crops have been marketed without FDA clearance, subject only to the general responsibility of

the food company to assure the safety of the food, e.g., conformance with the adulteration provision of the FFDC Act. Food additives or substances which are added to foods or become constituents of foods, must be "generally recognized as safe" (GRAS), or the subject of an approved food/feed additive regulation.

Animal drugs are also regulated by FDA in much the same manner as human drugs. In addition to proving target animal safety and efficacy a sponsor must also demonstrate that the drug does not produce harmful residues in edible food. An additional difficulty for those involved in the animal health field is that there is a split of jurisdiction between FDA and USDA, with FDA regulating animal drugs and some diagnostics and USDA regulating animal biologies and some other diagnostics. How ones' product is categorized has significant ramifications, with respect to which agency regulates, as well as to how the product is regulated.

THE REGULATORY ROADBLOCK?

While the Framework has permitted significant progress since its adoption in 1986, major uncertainties exist with regard to the future. These uncertainties will need to be resolved before one working in the field can have any reasonable degree of assurance that a safe product will be allowed to reach the marketplace on a timely basis and become a success or failure, depending on its value to the consumer. In my view, three things must happen so that the regulatory process does not become a roadblock.

The first is establishment of clear jurisdictional lines. While many of the questions as to "who" regulates the "what" have been decided with respect to field testing, significant questions remain unanswered regarding large scale testing and commercial approval. For example, it is unclear who will regulate commercialization of transgenic crops with enhanced pesticidal properties and how food and feed tolerances will be set. No clear policy has been articulated for transgenic animals. Questions also remain about the scope of the organisms subject to initial or commercial oversight.

A regulatory roadmap would give the regulated industry, the scientific community, public interest groups and consumers answers to questions—who has jurisdiction, how that jurisdiction will be exercised, and what is expected in order to obtain regulatory decisions.

Second is credibility. The agency charged with the responsibility must be able to render a credible decision. As an initial matter, the agency must have the necessary expertise. The regulatory process also must allow for appropriate public participation of decisions and communication of results.

A significant question yet to be answered is whether the regulatory process will focus on safety and efficacy, or whether the regulatory process will become the place for protracted debates about potential social and economic implications of the technology. This question is an essential one for the agricultural sector where the primary debate about products like bovine somatotropin have very little to do with safety and more to do with potential questions about the changing structure of agriculture.

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Third is timeliness; can the agency make the decision on a timely basis? As an initial matter, the agency must have sufficient resources. The agency's process must also provide reasonable time frames for decisions. A decision that takes an unnecessary amount of time, particularly in an area where the technology is moving rapidly, benefits no one.

CONCLUSION

As I have discussed, I do not believe that regulatory processes will be a roadblock to agricultural biotechnology in the long term. However, in the short term, the pace of approval of the products of agricultural biotechnology will be slowed by uncertainty.