



# IMPACTS

## of BIOTECH REGULATION on SMALL BUSINESS and UNIVERSITY RESEARCH:

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### Possible Barriers and Potential Solutions

PROCEEDINGS OF A "ROUNDTABLE" DISCUSSION SPONSORED BY THE PEW INITIATIVE ON FOOD AND BIOTECHNOLOGY AND THE UNITED STATES DEPARTMENT OF AGRICULTURE ANIMAL AND PLANT HEALTH INSPECTION SERVICE, JUNE 2-3, 2004, WASHINGTON D.C.



PEW INITIATIVE ON FOOD  
AND BIOTECHNOLOGY



USDA ANIMAL AND PLANT  
HEALTH INSPECTION SERVICE



# Introduction

MUCH OF THE UNDERLYING TECHNOLOGY that made the current commercial products of agricultural biotechnology possible was developed by small business and university-based innovators, and the scientists in these laboratories continue to push the technology forward. As we move towards the next generation of biotech products, however, some observers are concerned that our regulatory system can make it difficult for smaller enterprises to bring new products of that research to market. While most stakeholders generally agree that a clear and comprehensive regulatory system is necessary to ensure safety and to promote public confidence in the products of biotechnology, some have argued that the costs associated with compliance and the level of expertise required can put small business and university developers at a disadvantage and hinder introduction of smaller market products.

To illuminate these issues, the Pew Initiative on Food and Biotechnology and the U.S. Department of Agriculture's Animal and Plant Health Inspection Service co-sponsored a two-day workshop entitled Impacts of Biotech Regulation on Small Business and University Research: Possible Barriers and Potential Solutions. This workshop brought together a small group of experts representing a range of perspectives to examine the ways in which regulatory policies may have a disproportionate impact on small business and university innovation, and to consider possible avenues for addressing those concerns.

The views that emerged from the workshop are gathered here to help shed light on and provide direction for future exploration of these important issues. The exchanges among participants described here reflect only the opinions of the individuals present and not necessarily those of the sponsoring organizations.



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# Executive Summary

THE UNITED STATES DEPARTMENT OF AGRICULTURE is currently re-examining the way it regulates genetically engineered (GE) plants and animals. Since 1987, the department, through its Animal and Plant Health Inspection Service (APHIS), has reviewed some 10,000 genetically modified organisms and deregulated more than 60 GE plants.

The rethinking of the regulatory process is prompted in part because agriculture biotechnology is rapidly changing. Once focused mainly on improving the agriculture performance of major crop species—such as corn engineered for herbicide tolerance and soybeans engineered to produce their own pesticide—GE techniques are now being used to produce plants capable of making pharmaceutical and industrial compounds. Also in the pipeline are new GE animals and insects. USDA has said it wants to make sure its regulatory system is prepared to meet the challenges posed by these novel products.

Another important aspect of its comprehensive review will be an effort to modify or eliminate what some may view as excessively burdensome regulations and practices to assure that requirements are appropriate to the hazards identified. USDA has promised to consider the extent to which regulations and review processes can be revised and clarified so that the agency continues to protect plants, animals, humans, and the environment from any health and safety risks posed by GE products, but in a way that reduces both the length and cost of the review.

A more efficient, transparent, predictable and science-based regulatory process is of particular interest to small business and university researchers. Officials in both arenas have observed that under the current scheme, the cost of compliance is so high and the time it takes to get regulatory approval so long that potentially beneficial—and safe—plant and animal GE applications never make it to market. In addition, it should be clear how increased or changed regulatory requirements relate to safety and risk reduction.

There also is a concern that regulatory impediments could be damaging to the industry as a whole, since commercial applications of biotechnology are frequently first developed in either small companies or universities, as opposed to large, deep-pocketed corporations. Universities and small businesses warn that the field will not progress if the industry's incubators of innovation continue to be stymied by regulatory requirements. Future products that could mitigate some of the potential risks that trouble opponents of GE species or products that provide desired new benefits to consumers may be particularly at risk, as these innovations would be expected to be born in small business and university laboratories.

In an effort to understand more about small business and university encounters with the regulatory review process, the Pew Initiative on Food and Biotechnology, in partnership with APHIS, convened a roundtable to discuss various concerns related to existing regulations for agriculture biotechnology—the way they are implemented and the potential for changes to the status quo.

Participants included officials from small biotech firms currently seeking regulatory approval for GE products, venture capitalists evaluating potential investments in plant and animal biotech companies, and university officials involved in plant and animal research. They were joined by government officials from USDA, along with officials from the Food and Drug Administration (FDA), an agency that also plays a key role in the regulatory review of GE agricultural products.

Officials from small biotech firms discussed how regulatory uncertainty may be dampening investor interest in the field. Concerns about uncertainty are particularly acute for new applications of biotechnology, such as genetically engineered animals, where the regulatory structure is still being determined and the pathway to the marketplace is unclear.

Several participants said that the cost and length of the review process has made it particularly difficult to commercialize transgenic varieties of so-called small or “minor” crops, which include most types of fruits and vegetables and ornamentals with many potentially beneficial applications. They noted that these crops—while they may not produce revenues on par with major commodity crops like corn and soybeans—are still commercially important to many growers who could realize financial benefits from access to GE varieties.

Regulatory burden is also viewed as one factor impeding field research and commercialization of GE plants and animals by university scientists. Several university officials pointed out that academic scientists are generally not trained to deal with regulatory issues and perceive the process required to obtain approval of GE organisms as particularly complicated. And since career advancement is not dependent on finding commercial applications for their discoveries—in fact, the academic culture largely rewards the pursuit of basic research—fewer and fewer university scientists are submitting applications for regulatory review.

The roundtable produced a number of options to consider for improving the regulatory process. In general, there was agreement that better guidance from agency officials, particularly in regard to GE animals, about what it takes to get approval could reduce costs and uncertainty. Also, some company and university officials suggested that once regulators deem a particular plant modification to be safe, they could then allow the technology to be applied to other varieties of the plant without requiring approval for each new transformation, as is now the case.

In addition, there was discussion of creating some type of research consortium loosely modeled on a USDA program that provides technical support for securing approval of pesticide applications to small-acreage crops. Such an entity could, among other things, generate publicly accessible baseline data addressing safety concerns related to new GE organisms.

Regulatory officials from USDA-APHIS and FDA agreed to consider the options as part of their ongoing effort to overhaul their approach to GE plants and animals. But they said in the meantime, agency officials would be interested in continuing the dialogue about reducing regulatory burden and that certain actions that might help universities and small business, such as drafting new guidelines, could be implemented relatively soon.

# Section 1

## SMALL BUSINESS, UNIVERSITIES AND THE COMPLEXITIES OF COMPLIANCE

When small businesses or university researchers want to take a GE organism from the lab to field testing and then on to the farm, so to speak, the regulatory requirements they face are no different than what large companies encounter. And officials from small business and universities participating in the roundtable said that in pursuing changes, they were not seeking “special treatment.” When it comes to demonstrating that a particular GE plant or animal will be safe for plants, animals, humans and the environment, they agreed that regulators should demand no less from small companies and universities than they do from large agribusiness concerns.

Nevertheless, they observed that the burdens associated with obtaining regulatory review—namely the cost, length and uncertainties of the review process—can weigh more heavily on small companies and universities. As several participants in the roundtable noted, a key difference is that, unlike most large companies trying to commercialize GE applications, small companies and universities lack the staff and resources required to navigate the system.

### Regulatory Uncertainty and its Effect on Investors

As is often noted, GE technology now used in agriculture applications is relatively new and constantly evolving. The same can be said of the regulatory process that is intended to assess whether GE organisms are, for example, safe for the humans and animals that may eat them or for the surrounding environment where they may grow or (in the case of GE animals) feed. For a small business trying to bring a product to market, a changing landscape of regulatory review introduces a significant element of uncertainty.

Officials from many small companies said they are constantly struggling to understand precisely what they need to provide regulators to give assurances that their GE innovations will pose little risk when released into the environment. More to the point, they said the uncertainty about whether or when a product will receive approval now stands as a major impediment to attracting investment necessary to keep their companies alive.

One venture capitalist who specializes in agriculture biotech start-ups said regulatory uncertainty is an area of risk for which investors have little tolerance. He said that in general, before an investor considers backing a start-up, regardless of the product involved, they want to know all they can about risks

## WHAT DO VENTURE CAPITALISTS DO?

- Provide risk capital to early stage companies
  - Approximately \$10 billion invested in biotech each year
- What we look for:
  - Great management
  - Disruptive technology with strong IP
  - Large markets
  - Definable or well understood risk
- Investments
  - \$250,000 – \$10 million in return for equity in the company
  - Provide insight to build value
- Exit in 3–5 years
- Expect returns of >50% IRR
- The driver of innovation, unique advantage of the U.S.

## WHY IS VENTURE CAPITAL IMPORTANT?

- Small companies are the source of innovation
- Small companies are the path for commercializing basic research
  - Acquired by large companies
  - Technology transfer via partnering
- Small companies need risk capital
- A means of leveraging R&D spending and the sharing of risk for technology development
- Small companies are the source of job creation

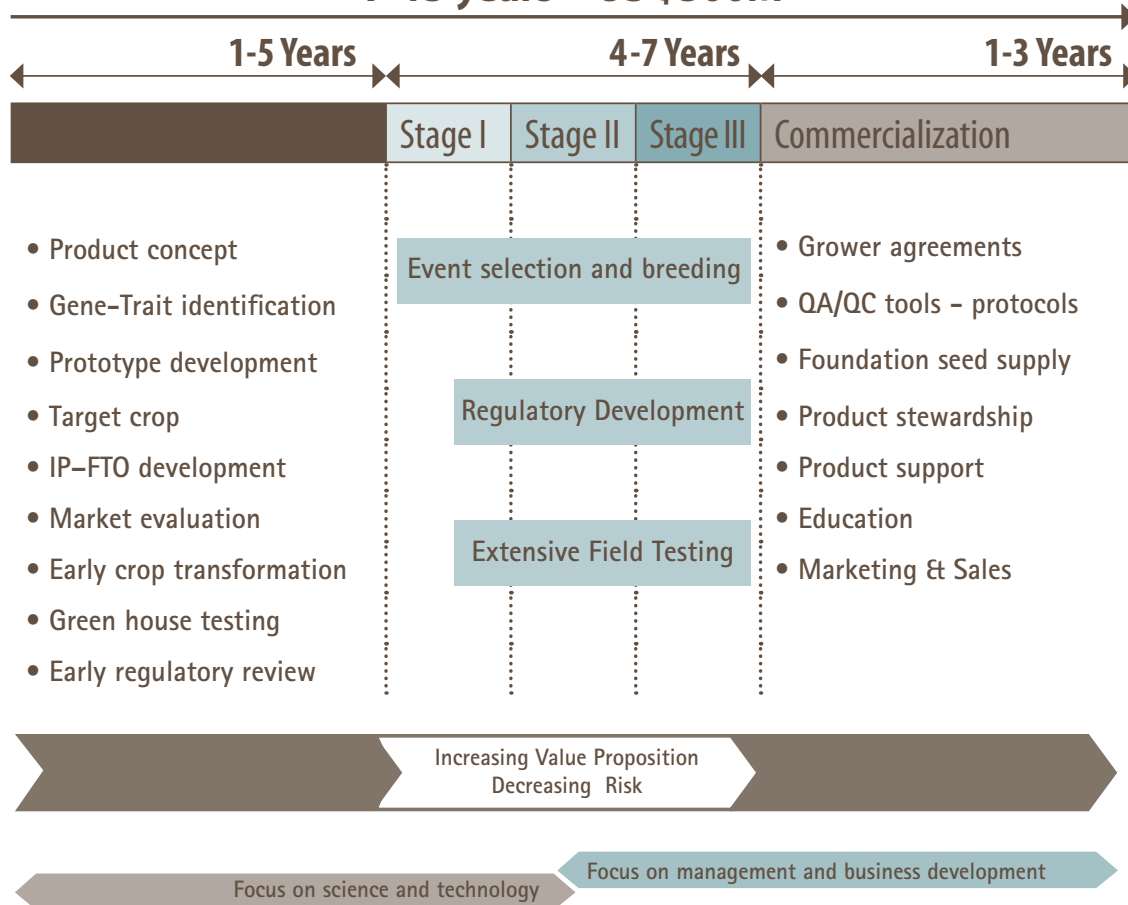
*Adapted from a slide prepared by Roger Wyse, Burrill & Co.*

related to getting a return. It's not that they are unwilling to assume risks. They just want a clear and thorough assessment of what the risk related to the regulatory process entails.

In that sense, an investor's analysis of the regulatory environment facing GE agriculture applications would focus not so much on whether the process is particularly demanding, but on whether those demands can be clearly understood and, in particular, how they relate to safety. In fact, a rigorous process could be seen as adding value to a company, he said, since regulatory approval would provide evidence that safety considerations have been given a thorough, objective review by an independent entity. But he said investors seek assurances that the process is "transparent, predictable and science-based."

## DEVELOPMENT PIPELINE FOR AG-BIOTECH TRAITS

7-15 years ~ US \$300M



He said the regulatory environment for GE agriculture applications has come to be viewed by investors as so complicated and uncertain that few are willing to put money in small companies. They don't believe they can sufficiently assess the odds that a product will get approved or, even if approval seems likely, they are unable to forecast how long the review will take and how much it will cost.

"Investors in this space, if we understand the risk, we can value the company and we can feel comfortable about investing," he said. "But if the regulatory environment is changing or is unpredictable—so that when a company comes in to get their product approved, it's not clear what the process is—we will not invest."

For example, he said for companies in certain market segments—namely those involved with new products such as GE plants that produce pharmaceuticals or GE animals in general—the regulatory environment has become so confused that investors are practically nonexistent.

"I would say if you are trying to produce a protein in a food crop, you have no chance of raising any money to do it," he said.

In general, officials from small companies said there is little interest in avoiding regulatory hurdles by taking their product to another country because regulatory standards may not be as rigorous. Most companies want a global market for their products, and given the political and consumer controversy surrounding agricultural biotechnology, they don't want to be seen as skirting regulations. One official said his firm has established a policy that it "will conduct no field trial and produce no product in a country whose standard is lower than" the U.S., Europe or Canada.

An official from a Canadian consortium developing a GE animal said that while the technology he's involved with could be particularly beneficial to large livestock operations in developing countries—the transgene cuts down

## ESTIMATING THE COST OF COMPLIANCE

Roundtable participants who work with small agriculture biotech "start-ups" estimated that expenses related to obtaining regulatory approval for a GE plant can represent "half the cost" of bringing a product to market. One company official said his firm already had invested a third of its start-up capital in regulatory compliance and that the process was not yet complete.

Participants said that it was hard to put a precise dollar figure on regulatory expenditures because there is not a shared view of precisely what should be counted. Some estimated costs to be in the hundreds of thousands of dollars, others in the millions.

on pollution by reducing phosphorous in the animal's waste—the animal will not go on the market until it passes muster with Canadian authorities.

“We are not going to be perceived as dumping a technology in a lesser developed country,” he said, adding that the goal is to “approve it in our own backyards first and then move it out.”

## Differences in Regulatory Burden between Small Companies and Universities and the Effect on University Technology Transfer

In some ways it would seem that university-based scientists are in a better position to deal with the challenges of getting regulatory approval for agriculture biotechnology applications.

As several company officials noted, unlike a small start-up, university researchers do not rise and fall based on whether or not their innovations receive regulatory approval. So from the small company perspective, in the university setting there is little risk related to failure. In addition, university researchers may have graduate students and post-doctoral candidates working in their programs who can help generate data needed to address regulatory concerns far more cost-effectively than can a company's scientific staff.

Yet university officials said that regulatory uncertainty also is discouraging their scientists from seeking approval of new GE innovations, though the dampening effect is different and, in some ways, more complicated than it is for small business.

One problem is that while university investigators may be quite astute when it comes to understanding science and technology, regulatory matters are not their area of expertise. One university official said that in general there is a “real ignorance in the academic setting about what regulatory affairs are all about.” Another official talked about the disconnect as a “90-10” issue: He said roughly 90 percent of academic researchers have no interest in commercializing discoveries and of the ten percent who do, about 90 percent of them have relatively little knowledge of the business world.

### CHARACTERISTICS OF SMALL BUSINESS INNOVATORS

- Limited employee base, variable expertise in development
- Good knowledge of technology
- Limited knowledge of regulatory affairs
- Limited capital
- Market driven
- Industry specific connection

### CHARACTERISTICS OF UNIVERSITY INNOVATORS

- Limited employee base with good infrastructure and expertise
- Superior knowledge of technology
- Limited knowledge of regulatory affairs
- Limited knowledge of business
- Limited capital
- May or may not be market driven (public goods)
- Limited industry specific connections

*Adapted from a slide prepared by John Kelly, MaRS Landing, University of Guelph.*

Regulatory approval is not of primary importance to the university researcher. For example, one official noted that while university scientists have been encouraged, particularly by Congress, to translate their discoveries into commercial applications, it is not the mainstay of their mission.

Moreover, the trend today in academic research is to focus on the basic biology of plants and animals, not on specific agriculture applications. University officials said academic researchers are more likely to reap professional rewards when their work leads to a better understanding of the underlying biological mechanisms of plants and animals, as opposed to a commercial product. For example, while a university researcher may end up creating various GE organisms, the goal of the work may be to understand something about basic protein function, not to develop a new plant or animal variety with commercial potential.

Furthermore, one university official observed that the academic culture surrounding plant breeders, in particular, tends to be “very informal.” Plant breeders working with GE technology may not always have in place the procedures necessary for maintaining the kind of documentation that regulators generally want to see.

Costs associated with the regulatory process were also cited as a factor behind university disinterest in regulatory approval. As one official pointed out, most academic researchers generally feel strapped for cash and may view any money invested in a regulatory approval process as consuming funds that could be better spent on research projects.

In addition, there may be institutional issues at play. While technology transfer can bring monetary rewards to institutions, it can also bring on recurring costs in the form of the fees required to maintain patents. One university official said his institution was already “purging” many patents on discoveries because it can no longer afford maintaining so many.

Overall, university officials described an environment with a considerable amount of built-in resistance to engaging in regulatory approval processes in general. And one university said the process for getting approval of a GE plant or animal is viewed by academic investigators as especially onerous.

“I think they are so afraid now of the regulatory process, they don’t even want to stick their toe in that morass,” he said.

A USDA official said that he has observed a steep decline in academic researchers’ seeking regulatory approval for GE innovations. While he said they haven’t

## NEW SCIENCE CHALLENGES OLD REGULATORY REGIMES

One of the reasons companies and universities may be finding it difficult and confusing to gain approval of GE agriculture applications is that, in general, federal agencies are subjecting them to review processes rooted in regulations and authorities that predate the field. The result has been a certain amount of confusion as regulators figure out how a system developed before the emergence of transgenic plants and animals should apply to these innovations.

For example, an official with a company seeking to develop a GE farmed fish that can mature faster than conventional varieties discussed the issues he has encountered in trying to secure approval from the Food and Drug Administration, which has decided GE fish must meet standards that were developed for the approval of new animal drugs.

As the company official noted, the regulatory standards required for his transgenic fish are in many ways "no different than those placed upon a drug developer...for a new cancer drug." But he said the processes required to generate regulatory information for a drug, a compound usually developed in a laboratory, are not necessarily adaptable to situation in which the "drug" in question is a fish growing in a pond or an ocean pen. "The reality is that the classical experimental design to identify this information is simply not available to us," he said.

He said FDA has been sympathetic to the fact that his company is sort of the "guinea pig" in the regulatory system and that it must come up with protocol designs that will be quite different from the experiments normally done to secure new animal drug approvals. But he said the basic uncertainty remains: precisely what it will take to satisfy regulators that a GE fish has met the standards normally applied to new animal drugs?

"While we have been through this interactive process and while we have completed the research and have spent well over a million dollars on the process, we honestly don't know whether what we've done is going to be adequate," he said.

Another company official discussed the evolution of FDA's ongoing effort to adapt existing regulatory authority to its assessment of human, animal and environmental safety concerns related to GE plants that produce pharmaceutical substances. In particular, he said it was a "bit of a shock" to companies trying to commercialize "plant made pharmaceuticals" or PMPs when the agency decided that farms used to grow these plants would, for regulatory purposes, be required to meet the same standards as a drug manufacturing facility.

"Those two worlds," he said, "are very, very different" and for small companies developing PMP's, regulatory compliance is going to be "very, very tough to deal with."

quite “disappeared off the radar scope,” when the agency first began its regulatory review of GE agriculture products, “it was not unusual for 20 to 25 percent of the submissions to be from the academic community,”

“You watch the numbers and it’s pretty evident that there are some underlying reasons why the academic community is dropping out of the picture,” he said.

## Potential Market Impact of Regulatory Burden

If the costs and uncertainties of the regulatory process are inhibiting small business and universities from commercializing GE products, how is this affecting the market?

Those involved with companies trying to commercialize GE agricultural applications noted that in the world of agriculture biotechnology, as with technology in general, innovation is usually driven from the bottom. It is the small start-up, frequently connected in some manner to a university, that serves as the incubator dedicated to taking the latest scientific breakthroughs and translating them into commercial applications.

Even though a breakthrough technology may ultimately be associated with a large corporation, it is usually a small business that first develops the idea, which the large company adopts by acquiring the smaller company.

Participants pointed out that the GE products now widely used in agriculture are innovations that were first developed by small companies over 15 years ago. And if the field is to move beyond the relatively small number of GE agriculture applications now commercially available—and develop products that offer clear benefits to farmers, consumers and society—then small companies, they said, will need to maintain their role in the chain of innovation.

But according to industry experts, the number of small companies operating in agriculture biotechnology is dwindling. Their depleted ranks are evident in the fact fewer small companies are forging partnerships with large agriculture biotech companies and fewer companies are conducting field trials of GE agricultural products.

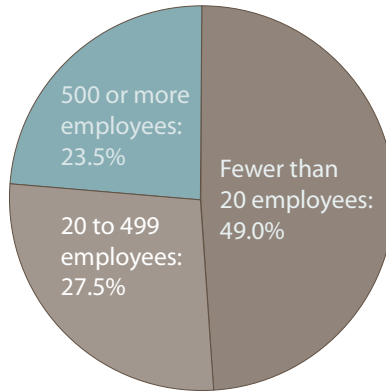
One area that may be feeling the effects of this dearth of innovation is the market for what are known as small crops or minor crops, such as fruits and vegetables and ornamentals. Though they may be grown in areas as small as 20 or 30 acres—much less than the thousands of acres typically devoted to

## HISTORICAL JOB CREATION BY SMALL BUSINESSES

Share of Net New Jobs, by Employment Size of Firm, 1990–1995

Small Business\*  
accounted for  
76.5% of new  
jobs created.

\* Small Business  
= Firms with  
fewer than 500  
employees.



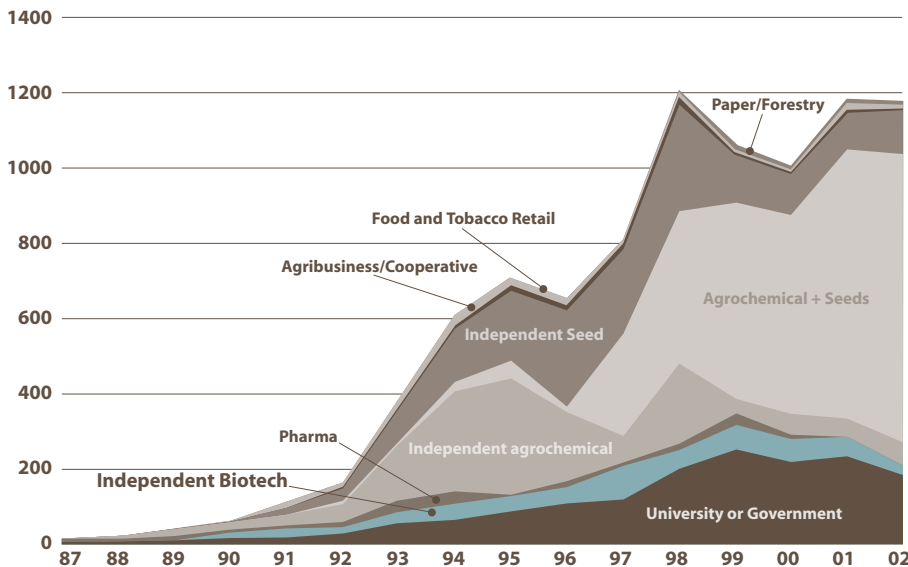
Source: SBA, Office of Advocacy, from data provided by the Bureau of the Census.

Adapted from a slide prepared by Roger Wyse, Burrill & Co.

## INDEPENDENT BIOTECHS: FEWER FIELD TRIALS

U.S. Field Trials of GM-Crops

Bio-Economic Research Associates-2003



Adapted from a slide prepared by Roger Wyse, Burrill & Co.

commodity crops such as corn or soybeans—one agency official estimated the combined value of specialty crops at \$45 to \$100 billion. He also observed that in 23 states, 50 percent of the agriculture income is derived from specialty crops, making this market segment very important to many state economies.

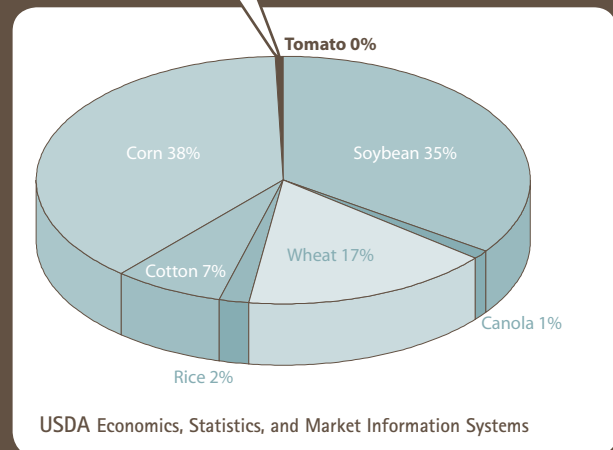
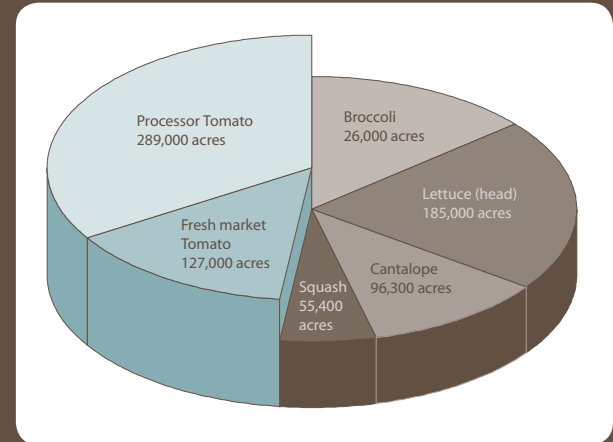
But there are very few GE varieties of specialty crops available and, according to several participants, the regulatory process is largely to blame. It's not just that their relatively small acreage makes companies unwilling to invest in approval. There are market variables and scientific issues peculiar to specialty crops that magnify the regulatory impediments.

For example, the length of the regulatory review can be particularly inhibiting, since many types of specialty crops may only be around for a few seasons before they are replaced by new varieties that have a greater market appeal. One participant recounted an effort initiated in 1989 to take what was then a popular variety of cantaloupe called the Mission melon and genetically modify it to make it resistant to a damaging plant virus. But in the time it took to generate the data needed to satisfy regulatory demands, the Mission melon had fallen out of favor. So a GM version no longer had much economic value.

The fact that reproductive processes for many fruits and vegetables are quite different from that of commodity crops like corn also can make regulatory approval cumbersome for specialty crops.

Today, when companies produce a new version of GE corn, and the transformation is approved by regulators, they can then add the new GE trait, such as herbicide resistance, to many different varieties of corn by simply cross-breeding the GM version with whatever type of corn they feel would benefit.

## CHARACTERISTICS OF SPECIALTY CROPS vs. THE AGRONOMIC CROPS PLANTED IN 2002



USDA Economics, Statistics, and Market Information Systems

*Adapted from a slide prepared by David Tricoli, University of California, Davis.*

But for most fruits and vegetables, the biology of the plant makes it impossible to incorporate the trait in different varieties through cross-breeding. Instead, scientists must create a GE version or GE “cultivar” for each different variety. And the number can be quite large, considering, for example, the many types of apples that may be grown in a single commercial orchard.

The regulatory concern comes in to play because USDA views each new cultivar as a separate “transformation event” that requires a separate approval.

Therefore, if a company created a GE apple and wanted to apply the same trait—with the same transformation technology—to 15 varieties of apple, it essentially must get approval for 15 different products. Each variety would be viewed as having been created through a separate “transformation event.” In contrast, a company producing GE corn with herbicide resistance may only have to submit one “event” for approval but can then, through cross breeding, transfer the new gene to many varieties of corn.

There are scientific reasons agency officials would want to look at each GE cultivar of, say, an apple, even if it involves the same gene. For example, there could be a concern that each transformation may have a different effect on the plant depending on how the new gene is incorporated into the plant’s genome. But the effect on producers is that the cost of getting approval for multiple transformation events has greatly diminished interest in using GE technology to incorporate potentially beneficial traits into fruits and vegetables.

One official said some commercial fruit and vegetable growers have been “highly keen” on using biotechnology to improve their products, given the need to stay competitive with foreign growers. But he said the regulatory costs are prohibitive. For example, an effort to use GE technology to add herbicide resistance to lettuce was abandoned because it would have required obtaining approval for 30 different cultivars.

# Section 2

## RESPONDING TO THE CHALLENGE: OPTIONS FOR CHANGE

THE MAIN FOCUS OF THE CONFERENCE was how to deal with the burdens cited by participants while still maintaining the integrity of the regulatory review process. Essentially, it could be said that three key challenges emerged.

One was how to address the burden of uncertainty in the regulatory review process. Here participants focused on the problems that stem from a sense that requirements are poorly defined, which means that business and university innovators have a hard time envisioning the path to approval. And if the regulatory environment is perceived as being rife with unknowns, investors are loath to spend their money on agriculture biotech start-ups and universities are unwilling to allocate scarce resources to seeking product approvals.

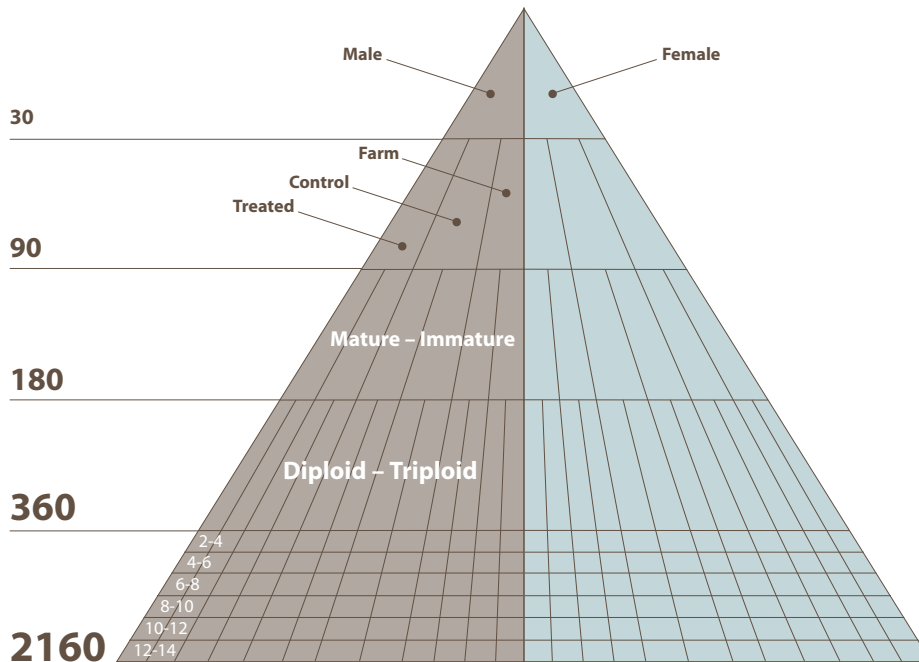
The second challenge focused on how, even if the regulatory requirements are crystal clear, small business and universities can deal with the burden related to the considerable data agencies require to assess safety. Producing such information can entail the conduct of costly and lengthy field trials that must be carefully and systematically monitored. Participants discussed different approaches to meeting this challenge and the difficulties with implementing various options.

Finally, there was discussion of reducing the burden through structural changes to the review process and modifications to the regulatory requirements themselves. Policy options focused on such issues as developing different stages of approval in the process that would give an indication of progress. There was also a suggestion that regulators should help spur the approval of more GE varieties of minor crops by revisiting their requirement that each transformation event be approved separately.

### **Reducing Uncertainty in the Regulatory Process**

Participants offered several suggestions for changes that could make regulatory review more predictable and hence less likely that confusion about regulatory requirements would discourage investors from seeding capital in biotech start-ups and university researchers from commercializing their work.

## EXPERIMENTAL DESIGN: A CLOSER LOOK



Classical experimental designs may not work for studying the safety of biotech animals. Using a classical experimental design, a developer of transgenic fish would need to look at the altered trait in various fish populations (mature vs. immature, diploid vs. triploid, control vs. treated vs. farmed, male vs. female, and all combinations thereof). This would require processing 2,160 fish or just under eight tons of fish in one day, an impossible task according to the developer. Not only is timing a limiting factor, but the sheer quantity of fish necessary is many times more than what is currently available.

*Adapted from a slide prepared by Joseph McGonigle, Aqua Bounty.*

	USDA	USDA APHIS PERMIT	FDA	GLPs	cGMPs	SOPs
Gene Isolation and Engineering	●	●	●	●		●
Transformation	●	●	●	●		●
Event Sorting	●	●	●	●		●
Master and Working Seed Banks	●	●	●	●	●	●
Production	●	●	●	●	●	●
Grain Processing			●		●	●
Antibody Extraction / Purification			●		●	●
Formulation			●		●	●

*Adapted from a slide prepared by Michael Pauly, Chromatin, Inc.*

These included the following:

- ◆ **Develop better agency guidance documents, particularly for emerging agriculture biotechnology applications, such as GE animals.**

Agency officials frequently try to address uncertainties surrounding product approval processes by developing official “guidance” documents. These documents do not contain legally binding requirements but can provide considerable detail as to what an agency will expect an applicant to provide in order to meet particular regulatory standards.

Several issues related to GE agriculture applications—such as the use of GE plants to manufacture pharmaceutical substances—have been addressed in guidance documents. Participants said additional guidance documents could be used as a mechanism to bring more clarity to the process. For example, many participants noted that regulatory requirements for GE animals are particularly unsettled and those seeking to commercialize innovations in this area are anxious to understand more precisely what kind of information regulators will need to satisfy health and safety concerns. It also was suggested that guidance documents could detail how applicants could use certain kinds of biological data already available in published, peer reviewed scientific studies rather than generating the information anew.

In addition, there was discussion of developing guidance documents that would more carefully correlate agency expectations to the type of GE innovations an applicant is submitting for approval. For example, agency guidance would discuss what it would expect for a new crop variety with a single GE trait versus an application related to a crop with multiple GE traits.

- ◆ **Reduce the number of data submissions required from applicants**

A related suggestion focused on the need to take steps that would reduce the frequency with which regulators return to applicants seeking additional data. One participant said that in general, applicants feel like they have to come back “again and again” to answer “more and more questions” from regulators and these exchanges turn into delays. There was general agreement that applicants need to work with agency officials to seek ways to get the cycle down to one data submission.

One way to do this, according to participants, is for agency officials and applicants to have a thorough discussion of expectations at the beginning of the process and to make use of communication technology—such as video conferencing—to facilitate these exchanges. An agency official suggested creating an initiative in which government regulatory experts would offer training sessions—for both small business and universities—that would deal with “how to go through the whole process.”

Participants also suggested that agency officials could identify “go and no-go” factors that would make clear specific situations in which a review would either progress or come to a halt.

As one participant noted, “the burden is on the producer to understand what the regulator needs and the burden is on the regulator to make sure the producer understands what they need.”

### **Generating Data to Support Safety Assessment**

Representatives from small biotech firms said they are particularly challenged to generate the considerable amount of scientific data required to satisfy regulatory requirements. Participants offered several recommendations that could make data demands less of an impediment to commercialization.

#### **◆ Enlist university researchers to conduct research addressing health and safety issues.**

Several participants observed that alliances between small businesses and agriculture-oriented “land grant” universities could make meeting the data demands of the regulatory process easier. The partnerships would focus on using university research facilities and expertise to conduct some of the field-testing required to assess basic environmental risks surrounding GE agriculture innovations. There could be impediments to having universities perform this role, including the fact that university researchers may in general have little interest in conducting research designed to answer regulatory questions. Furthermore, it was noted that providing data in support of a quest for commercialization could expose universities to liability claims should there be any mistakes in their assessments.

#### **◆ Create an a entity similar to the USDA's IR-4 program, which helps secure regulatory approval for pesticide use in small or “minor” crops, to speed product approval of relatively low-value GE crops.**

The notion of creating a government entity or public-private partnership to conduct the research needed to secure regulatory approval of GE minor crops was discussed at length by the participants.

Questions were raised about whether there is sufficient market demand for putting GE traits in things like fruits and vegetables or ornamental plants to justify the investment. One participant observed that the IR-4 program for pesticides has been successful because there was a clear “pent-up” demand in the market for having certain pesticides approved for a wider variety of uses. But he said it’s not clear where there is a similarly high demand for GE traits in minor crops. Participants agreed that a thorough market assessment of the need for such a program would be required before anything like an IR-4 program for GE applications could be justified.

Another participant responded that an IR-4-like program could be successful even if it did not push particular GE varieties all the way through the regulatory approval process. He said an entity that would put together the kind of data that simply would advance minor crops farther along the path toward regulatory approval could make them less risky, from a business standpoint. Therefore, companies seeking to commercialize GE versions of minor crops would be more likely to attract investors.

◆ **Provide a detailed template or example of the data submitted in a successful real-world regulatory review process.**

Participants said it would be useful to have data from successful applications for approval that would provide tangible examples of what companies will be required to submit. However, it was noted that releasing up-to-date information on successful applications could be a challenge, given the fact that agencies are legally prevented from disclosing data designated by applicants as “confidential business information” or CBI, which frequently covers much of their submissions.

## **Structural and Substantive Changes to the Regulatory Process**

Several of the suggestions for reducing regulatory burdens addressed the regulatory requirements themselves and the structure of the review process. These included the following:

◆ Consider modifying the requirement that each GE transformation 'event' undergo a separate assessment of its health and safety risks.

As was noted previously, representatives from both universities and small companies say they have shied away from developing GE versions of minor crops in which each variety of a single plant type would have to be created by through a separate “transformation event.” That is because the biology of certain plants—chiefly fruits and vegetables—does not readily allow the gene to be transferred to different varieties through cross-breeding. Each variety or cultivar must be transformed separately and the regulatory requirements dictate that they must be approved separately as well.

As a result, it is much easier to get regulatory approval for a crop like corn, in which the transgene can be transferred to different varieties via-cross breeding, than lettuce, in which the only practical way to put the same gene in different varieties is to create a new GE plant for each variety.

One recommendation was for agency officials to reconsider the “unit of regulatory consideration” so that when producers are working with a single plant type—and using the same gene and transformation process for each variety—they would not have to get a separate approval for each plant or “cultivar” they create. It was acknowledged that agencies still would need to have a scientifically valid process for assessing whether the individual cultivars—even if the gene and transformation technology are identical—have the same health and safety profile.

◆ Establish “milestones” in the regulatory process to offer an indication of progress toward commercialization

Participants noted that one way to remove some of the mystery from the regulatory process would be to change the structure of the system to establish clear “milestones” of progress that would demarcate various points between initial application and final decision, as is done in the review of prescription pharmaceuticals. For example, it was noted that as drug companies move from pre-clinical testing to Phase I, Phase II and Phase III clinical trials, their progress is acknowledged within the regulatory process and, for investors, each step along the way to approval becomes a “value creating event.” Participants suggested that something analogous could be considered for GE agriculture products.

### ◆ Offer conditional approvals of GE plants or animals

There was a suggestion that small companies might find an advantage to receiving a conditional approval of their GE product, which could allow them to put it on the market subject to certain use or time restrictions while they continued the process toward final approval. Such a process is sometimes used with new pesticide applications to allow registrants to gather additional data, typically to help clarify assumptions used in the initial assessment. Conditional approvals could allow a company to bring a product to market earlier than might otherwise be possible, generating additional revenues. On the other hand, some participants suggested that conditional approvals also extend the ultimate approval time and that the uncertainty of a final approval could represent additional risk in the eyes of investors. One government official noted that when his agency had queried companies about their interest in conditional approvals no one wanted them. “They wanted hands-off after approval,” he said.

### ◆ Charge applicants user-fees that would go toward overall improvements aimed at speeding review.

There was some discussion of creating user-fees to give agencies more resources to reduce regulatory burden, particularly by reducing the time required for reviews. However, there was a general recognition that establishing user-fees can be politically difficult. One government official noted that previous discussions of user fees in relation to the regulation of agriculture biotech have “run into problems.” It also was noted that user fees could add to the costs of regulation and end up being another barrier to small business and universities, although user fees can be structured in such a way as to reduce burdens on smaller entities.

### ◆ Restructure the process to establish different categories or “tiers” of review that correspond to magnitude of risk.

Participants discussed whether regulators could adjust the requirements for regulatory review based on the known issues surrounding a particular plant or animal transgenic trait or technology. Products associated with relatively high risks or large unknowns would be subjected to one level of review while those considered less risky would be allowed to proceed through a more rapid review.

## CONCLUSION

AGENCY OFFICIALS ACKNOWLEDGED that there is much about the regulatory review process for agriculture biotech that can seem “archaic and Byzantine.” But they also said it is important to remember that GE plants and animals are different than other types of regulated products in one key respect: at the end of the day most of them will be released into the open environment.

If the issue at stake was a permit to do “laboratory or contained research, the process would not be so daunting,” said one official. But the fact is that, be it a GE fish cultivated in an ocean pen or a GE crop growing in a farmer’s field, there is the potential that products of agriculture biotechnology will interact with the general environment in a potentially detrimental fashion. Those kinds of risks require that they be under “significant regulatory scrutiny,” and give rise to review processes “that are very new” to all concerned.

Another official also noted that regulatory processes will, to a certain extent, always seem burdensome due to the tension inherent between the regulators, who are focused primarily on plant, animal, human, and environmental health and safety, and the regulated, who, while not insensitive to these concerns, are most focused on finding the quickest path to market. It is not surprising, then, that conflicts arise between what a producer and regulator define as a risk and what they view as the appropriate data to assess that risk.

That said, the regulatory officials who participated in the discussion insisted that they are keenly interested in what they can do to make the process less intimidating to small businesses and universities. And they encouraged business and university officials to continue the dialog, formally and informally.

“Regulations are currently undergoing complete reevaluation all over the world, including in the United States,” said one official. “There’s a tremendous need for more outreach activity.”

Another agency official encouraged small business and university officials, on a more informal basis, to feel free to simply pick up the phone and call regulatory agencies whenever they have questions about the process. “We do encourage people to consider us to be a resource as well as a regulatory agency,” she said.

Some participants also wanted to be clear that regulatory approval is not the only obstacle preventing university researchers and small companies from developing more agricultural biotechnology products. Public acceptance of GE products also looms large.

One university official remarked that “regulatory burden is the least of the barriers to commercialization” and that the specter of consumer rejection is the most significant factor inhibiting the development of agricultural biotechnology. An official with an agribusiness supplier agreed that public acceptance is a major concern. But he said if the regulatory process was not so costly and time-consuming, his company would be much more likely to test the waters by bringing some new GE plant innovations to market.

Some participants said the regulatory process is strongly tied to public approval and wanted to see agency officials intervening when approved products are publicly attacked as unsafe and untested. Agency officials responded that they must walk a fine line between approving a particular GE variety and becoming an advocate for its use. Participants agreed that all involved—agencies, universities and small business—need to be more proactive in explaining the issues considered by the regulatory process and what a favorable decision says about the safety profile of a particular product.

Overall, there were no illusions that the policy options discussed here would solve all the difficulties small business and universities encounter as they seek regulatory approval of agricultural biotech products. However, there was agreement that the constructive dialogue could lay a foundation for more productive interactions between regulators and the regulated. In particular, government officials said some of the proposals that emerged during the roundtable could make their way into the ongoing review of the regulatory process. As one agency representative noted, government officials have set an “ambitious timeline” and are genuinely committed to relieving regulatory burden.

