Public Research and the Regulatory Review of Small-Market (Specialty) Biotechnology-Derived Crops Workshop

Proceedings

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USDA, APHIS (Animal and Plant Health Inspection Service), Riverdale, Maryland

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Executive Summary

Public Research and the Regulatory Review of Small-Market (Specialty) Biotechnology-Derived Crops

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Specialty crops, which include vegetables, fruits, nuts, flowering plants, nursery stock and other horticultural products, produce approximately 50% of US agricultural crop value (~$45 billion/annum). A decade after the introduction of genetic engineering (GE) into U.S. agriculture, however, it is clear that the biotechnology revolution is bypassing specialty crops. Relatively few GE specialty crop varieties have been submitted to regulatory agencies for clearance, and most of those that have been approved are not available in the marketplace today. Only one – a disease-resistant papaya – is a commercial success, and it was developed not by the private sector, but by public researchers. The number of products in development has declined rapidly over the last five years, and is approaching zero. Thus the outlook for change is bleak, unless those factors suppressing interest in GE specialty crops are identified and reversed.

It is widely understood that large investments of capital in small-market crops may be unprofitable, because of limited sales. A substantial fraction of development costs of GE crops goes to meeting the requirements of the U.S. regulatory agencies to demonstrate safety. Can the regulatory requirements be met by some different approaches that reduce costs but maintain safe products and effective regulation?

This two-day workshop was convened to discuss how the public research sector, the regulatory agencies, and the private sector can work together to facilitate the regulatory review of specialty GE crops. The workshop's objectives were (1) to identify major sources of cost and uncertainty in the development of GE specialty crops and submission for approval; (2) to identify research that can help meet these requirements effectively and at minimal cost, without compromising the integrity of the regulatory process; and (3) to learn about existing programs that facilitate commercialization of other regulated small-market products and recommend a model that would be useful for GE specialty crops.

Regulatory Agencies

There are three regulatory agencies in the United States that oversee GE crops: the United States Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) through its Biotechnology Regulatory Services (BRS) Division; The Environmental Protection Agency (EPA); and Health and Human Services' Food and Drug Administration (FDA). APHIS-BRS protects agriculture and the environment by evaluating genetically-engineered (GE) products that present a potential plant pest risk (including DNA from a plant pest, such as cauliflower mosaic virus), and oversees field testing. The EPA has responsibility for GE plants that raise pest management or pesticide issues protects the environment and food safety of GE plants that contain pesticidal proteins (such as the *Bacillus thuringiensis* delta-endotoxin [Bt]),

and FDA assures that food and feed derived from GE plants is safe and wholesome (nutritionally, allergenically, and compositionally)

The processes that each agency has developed for regulatory review vary according to each agency's mandate and the intended use of the product. To consider deregulation of a plant product, APHIS-BRS requires submission of data to demonstrate that release of a GE plant into the environment will not present a plant pest risk. This data submission usually occurs after several years of field. The EPA will approve GE plants with pesticidal traits only when there is a finding of reasonable certainty of no harm. This determination depends on input from expert advisory panels and from public comments. Again, extensive data must be submitted showing specificity of the pesticidal trait for the intended target pest (or if toxicity is broader, no meaningful exposure of other species), and no harmful residues of the pesticidal substance or its metabolites in food. The FDA evaluates data on the characteristic components of the food or feed in the form in which the product will be eaten to ensure that new products are safe as the foods that are currently on the market.

All of the agencies review products on s case-by-case basis. Each of the agencies depends on input from experts and provides opportunity for public comment. Reviews evaluate differences between the properties of the GE products and their conventional counterparts.

Identifying Economic Barriers

Speakers from the public sector described their experiences with GE specialty crops. The GE papaya resistant to papaya ring spot virus – currently the only commercial success – was developed in the public sector, with the private sector contributing no-cost licensing of the proprietary tools for generation of the GE plants. The process of obtaining regulatory approval was relatively straightforward. Another example, GE plum trees resistant to the plum pox virus, has been developed in the public sector and is currently being considered for deregulation. In both these cases, the major barriers to deployment were related not to U.S. regulatory agencies, but instead to industry structure and market needs. From inception to public release of the papaya required 20 years (only 7 of which were needed for field trials and regulatory approval). The GE plum is now (in 2004) at 13 years since inception of the project. During that time, preferred varieties and market needs change and researchers risk producing something that is obsolete when finally released. The situation is exacerbated in the floral industry for the same reasons. Although the regulatory process can be improved, there remain structural impediments in the specialty crop industries that limit the number of appropriate targets for use of biotechnology.

The other important economic barrier identified by all participants is overseas regulation. Most of these specialty products have export markets, and the lack of regulatory standardization around the world creates tremendous costs, inefficiencies, and uncertainties.

Characteristics of an improved and more efficient approach to regulation, which would maintain or even improve safety of GE products, are as follows:

- Traits evaluated across appropriate groups of plants (e.g., leafy vegetables) with the same trait, rather than event-by-event.
- A clear and consistent regulatory pathway, because breeding programs take a long time, especially for fruit trees.
- Distinction between products shown by experience to be relatively benign, and those that are more likely to present safety issues.
- Evaluation of GE products basing risk analysis on phenotype.

Although there are significant barriers to commercializing GE specialty crops, they are not without their advantages. Because they are grown on small areas, it is easier to maintain segregated product streams without admixtures, and to track the products, than for major commodity crops. Therefore the product being sold can be more reliably tailored to the needs of different markets and different regulatory systems.

Models for Overcoming Economic Barriers

Two functioning models were examined: The IR-4 Project, which aids in registration of pesticides for use on specialty crops; and the Orphan Drug Program, which stimulates private-sector development of drugs for rare diseases. Both address needs that would not be filled in the normal course of events, and both have been very successful.

The mission of IR-4 is to provide safe and effective pest management solutions for specialty crop growers. Funding comes from USDA (CSREES and ARS), the land grant university system, and the commodity and crop protection industries. The total value of the IR-4 Project is $25-30 million. This project receives and prioritizes requests for data to support extending the registration of existing chemicals to uses on specialty crops. Funds support field trials using the pesticides in question, and residue analysis in laboratories certified for good laboratory practices. Data are then submitted directly to EPA. This approach is highly successful because it is a fully cooperative partnership between academia (and ARS) and the crop protection industry. Of the 24 insecticides that EPA is currently considering for use on specialty crops, IR-4 has developed data for 23.

The Orphan Drug Program, housed in FDA, focuses on developing products that demonstrate promise for diagnosis and treatment of patients with rare diseases or conditions (affecting fewer than 200,000 people in the U.S.). It is broader than IR-4: its three main functions are administering the Orphan Drug Act, managing a grants program for clinical research on rare diseases, and managing the humanitarian use device designation program. Numerous economic incentives are available for private companies to develop these drugs, and the Program facilitates the evaluations, including difficult problems of running useful clinical trials when the patient population in very small. Before the Orphan Drug Act established this program, fewer than 15 drugs were approved for rare diseases. Twenty years after its passage, 256 drugs and biologics have been approved for rare diseases.

Facilitating approvals of GE specialty crops is different from pesticides or orphan drugs, so the rationale developing an organizational structure to address this issue needs to be considered carefully. Such an entity might reduce both the costs and the

uncertainties of meeting regulatory standards. Efforts targeted to consumer benefits (output traits) would be very likely to influence the climate of consumer rejection, but no business plan has been developed that envisions a profit from such traits in specialty crops. Having a facilitating organization could help. Because of the wide diversification of specialty crop industries, an extraordinary degree of partnership, cooperation, and broadly based support would be necessary to make this effort successful. What is needed includes the following:

- Streamline knowledge of what is required for regulatory decisions, so that development efforts can focus on that.
- Develop a network of laboratories within the public sector, somewhat analogous to the network of IR-4 research laboratories, but centered on product and molecular characterization and efficacy testing for regulatory clearance.
- Pursue products that have a clearly evident public need so as to better empower regulatory action.
- Engage nongovernmental organizations as allies in development of small market opportunities that serve the public good.
- Leverage regulatory knowledge across the public sector; develop public sector specialists in biotechnology regulation who can work with the proposed new entity.
- Leadership from stakeholders.

Recommendations from the Workshop

Extensive discussions among the participants, both in plenary sessions and in breakout groups, led to adoption of three major recommendations for action.

(1) Develop a plan, based on existing or new models, for an organization to facilitate the development of GE specialty crop products up to the point of regulatory approval.

Action: A steering committee was formed, consisting of volunteer participants from stakeholder groups (commodity and trade organizations) and university scientists, with participation also by USDA staff members. The committee will develop a concept paper for distribution to a broad group of stakeholders.

(2) Develop a research plan to identify needed data for regulatory consideration.

Action: This recommendation will be among the first tasks to be addressed by the proposed organization once it is developed and implemented.

(3) Prepare white papers for publication in internationally circulated peer-reviewed journals, assessing what is known about transgenic crops and the associated science.

Action: Volunteers from the workshop participants formed a committee to identify important topics for white papers and to suggest who might be best positioned to author them.

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PROCEEDINGS[1]

I. Introduction to the Workshop

Workshop Purpose

The purpose of this workshop was to discuss how the public research sector, the regulatory agencies, and the private sector can work together to facilitate the regulatory consideration of specialty (small/niche market) biotechnology-derived crops.

Workshop Objectives

Ann Marie Thro, National Program Leader, Plant Breeding and Genomics
CSREES-USDA

The urgency of our purpose in this workshop is conveyed by an article on "emergent issues" in biotechnology and agricultural research policy, by Fred Buttel, a sociologist at the University of Wisconsin. Buttel believed that "the adoption of industry agendas for biotechnology research will provide new ammunition to ... critics of public agricultural research, thereby creating unsavory publicity for the system." Buttel wrote that eighteen years ago. Today, there are indeed groups who have found ways to use biotechnology, in particular transgenic crops, to paint a negative picture of agricultural research.

As suggested in editorials in both Scientific American and Nature Biotechnology in the summer of 2004, transgenic crop varieties are needed from public research and small businesses, varieties that provide a range of different benefits, in different crops; varieties that solve problems for the environment, the economy, or individuals, or that create new opportunities. However, before a broader offering of transgenic crops can be presented to the public, they must be approved through a trusted regulatory process.

In 2002, the National Center for Food and Agricultural Policy (NCFAP) published a report (Gianessi et al, 2002.) on projected pesticide savings if all approved and pending transgenic crops were adopted. In 2003, NCFAP observed to USDA that poor market acceptance for transgenic crops appeared to be causing attrition among the pending opportunities for environmental benefit identified in their 2002 report. They suggested a workshop to highlight benefits from transgenic crops in USDA's research pipeline.

[1] The text below is based upon transcription of the actual presentations, questions, and comments.

In April 2004, at a planning meeting for such a workshop, the Steering Committee pointed out that the concern raised by NCFAP applies also to projects of USDA's state partners, the 1862 and 1890 land-grant universities; and to small businesses. To meet a need of all these entities, the Steering Committee suggested a more focused workshop, on navigating and funding the regulatory process, with special reference to small-market crops that face a significant disparity between costs of meeting regulatory requirements, and potential returns from a small market. While the focus was narrowed, the advisory committee was broadened, to include representatives of the additional partners, and a third USDA agency, our host today, APHIS.

Before listing the workshop's objectives, it may be helpful to review what are <u>not</u> the objectives.

- Intellectual property and freedom-to-operate concerns are set aside, to be discussed in other fora. The organizers appreciate that there are groups working on these questions, such as PIPRA, which is represented at this workshop.

- Market acceptance issues are also, to some degree, taken out of the discussion, by focusing on crops intended for the U.S. market. We are keenly aware that international aspects are important. One of the outcomes of this workshop may be follow-on activities to address these.

- We are further aware that the workshop may give rise to ideas that will be useful to the continued evolution of the regulatory process itself. However, this also is not the purpose of the workshop.

- The workshop is not intended to suggest that small market size justifies concessions in the scientific standards of the regulatory process.

Workshop objectives include:

- Identify current regulatory requirements that are major sources of cost; or of uncertainty, which creates costs;
- Identify researchable questions, the answers to which would help meet those requirements effectively and at minimal cost;
- Consider existing models that have enabled other small-market products, also subject to regulation, to complete the requirements necessary to come to market;
- Propose one of these models, or a new model, for small-market transgenic crops.

Anticipated achievements are:

- The target for the workshop is a set of recommendations for a concrete, do-able, fund-able model, one that will allow the regulatory process to work as intended for specialty crops, and thereby achieve market access for a broader range of approved transgenic varieties.

- The ultimate targeted outcome is a wider range of public-goods benefits than can be provided by major-market transgenic crops and private investment alone.

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Impacts of Biotech Regulation on Small Business and University Research: Possible barriers and potential solutions

Background synopsis of a workshop held June 2004 and
organized by the Pew Initiative on Food and Biotechnology (PIFB) and APHIS, USDA

Michael Fernandez, Director of Science, PIFB

This workshop focused on policy questions concerning the regulatory burden and small-business and university research. The motivation for the workshop came from the ongoing review of the regulatory structure governing the use of biotechnology in food and agricultural production, and the concern that a regulatory burden set too high may stifle innovation, particularly in small businesses and universities that have less capacity and less experience in dealing with regulatory agencies and systems. Proceedings from this workshop (Fernandez and Smith, 2005) are available on the website of the Pew Initiative on Food and Biotechnology, at:
http://pewagbiotech.org/events/0602/.

II. *Overview of the Current Economic and Regulatory Situation*

Moderator: *Dan Jones, National Program Leader, Biotechnology, CSREES-USDA*

Specialty Crops

Alberto Jerardo, Economist,
Economic Research Service,
United States Department of Agriculture

Specialty crops, which generally consist of vegetables, fruits, nuts, and other horticulture products. In 2003 these crops had a total sales value of about $50 billion, contributing about 25 percent of the total U.S. agricultural production value. Farm sales value in relation to other crops represents about 50 percent of total crop value in the United States, and in terms of trade, about 45 percent of agricultural imports and 24 percent of agricultural exports are specialty crops. Many of these imported specialty crops are off-season fruits and vegetables. These numbers indicate that specialty crops are not "small market" if viewed collectively.

The farm sales receipts of these horticulture crops total about $50 billion, representing 47 percent of all crops produced in the United States. Some individual vegetable crops are even larger than tobacco, which is one of the major field crops. Fruits and melons represent about $11.5 billion in farm sales receipts, and the share in total crops is 10.8 percent. One other large group is nursery and greenhouse crops, consisting of floriculture and Christmas trees, which represents about $15.2 billion, about 14 percent of all crops and second only to vegetables as a group.

Of the major vegetable crops in gross sales value by farms, potatoes (all types) lead the group at $2.6 billion, which represents about 15 percent of all vegetables. Lettuce is about $2.1 billion, which is about 13 percent of all vegetables in gross sales value. Tomatoes for fresh market and tomatoes for processing represent almost $2 billion and about 12 percent of total vegetable farm sales receipts.

Among fruits and nuts, the largest crop is grapes, representing $2.6 billion with about $1.5 billion worth of grapes made into wine; grapes represent 18 percent of all fruit and nut sales. The second largest crop is almonds, which is the number one U.S. export nut product. Other major crops are apples, oranges, strawberries, and melons. Other major specialty crops include nursery and other greenhouse crops at $9.5 billion, which includes vegetable transplants that are grown initially in greenhouses. Floriculture is the next largest crop, which represents about $5.1 billion.

Market price depends on a number of factors that can be condensed to four: supply, demand, competition, and quality. High yielding varieties and good weather increase the supply and depress prices at the farm gate, especially of commodity products. Competition increasingly comes from overseas producers, whose cost basis may be lower than in the U.S. Demand is also shifting, with increasing consumption occurring outside the home (now about half of all meals in the U.S.). In response, U.S.

farmers must reduce input costs (for example, by planting seeds of improved quality or using more efficient production practices), or they must produce unique materials or materials with quality traits that set them apart from commodities and bring a higher price. Good weather, competition, and shifting consumption patterns are beyond the control of the farmer. The quality of plants and seeds and the quality of products are where biotechnology can make a difference.

As an example of individual crops and how the cost of the seeds or transplants relates to total variable cost, in Michigan, potatoes are used for manufacturing foods or making potato chips. Out of the total $2,392 in variable costs per acre, $275 is the cost of the seeds, which is 11 percent; but pumpkin seeds represent 3 percent of variable costs for that crop because pumpkin farmers use only seeds, not plants. In contrast, for blueberries, the percent of variable costs is much higher because blueberry farmers use transplants (not seeds), even though those plants are viable for a number of years.

Regulatory Considerations of Small-Market Biotechnology-Derived Crops

Sally McCammon, Science Advisor, *Biotechnology Regulatory Services*
Animal and Plant Health Inspection Service
United States Department of Agriculture

The United States Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) formed Biotechnology Regulatory Services (BRS) in 2002. Prior to that, APHIS had an organization called Biotechnology, Biologics, and Environmental Protection that was disbanded in 1998 with many of its functions integrated into other parts of APHIS. However, because of subsequent increased national and global interest in biotechnology and biotech regulation, APHIS reconstituted its organization and did this based on an internal review process. The stated purposes for establishing BRS were to keep pace with the evolving technology and to assure that the resources were dedicated and capacity increased to address the multiple issues that had arisen. APHIS-BRS was to enhance the science basis of the APHIS regulatory program and ensure that the regulatory program would be both rigorous and reasonable.

A variety of traits are being introduced into plants. These include agronomic improvements in pest protection such as *Bacillus thuringiensis* (Bt) protein-mediated insect resistance and virus resistance; yield improvement; herbicide-tolerant crops; environmental adaptations such as drought and salt tolerance; product quality improvements; and pharmaceutical proteins.

Three major agencies review these products- APHIS, the Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA). APHIS is responsible for overseeing the field testing and release of plants into the environment as well as ensuring that the products do not present agricultural and environmental safety issues. EPA reviews pesticidal products to ensure environmental and food safety, and FDA assesses the safety of the whole food. Which agencies review a particular product depends on the intended use of the product. For instance, a viral-resistant trait in a food crop will be reviewed by all three agencies. Herbicide tolerance in a food crop will

be reviewed by APHIS-BRS and FDA, with EPA overseeing the use of the herbicide. Herbicide tolerance in an ornamental crop will be reviewed by APHIS-BRS, with EPA overseeing the use of the herbicide. Modified oil content in a food crop will be reviewed by APHIS-BRS and FDA, whereas modification to an ornamental flower crop will be reviewed only by APHIS-BRS.

APHIS-BRS regulates these products under the Plant Pest Act of 2000. Plant variety development goes through several stages—from the laboratory through early field testing and line selection, variety development and finally into commercialization. APHIS-BRS regulates primarily in the field testing, pre-commercialization stages.

The products reviewed by APHIS-BRS are called regulated articles and have some plant pest attribute: the vector may be a plant pest, such as Agrobacterium, a gene or regulatory element may be inserted from a plant pest such as cauliflower mosaic virus, or a gene may be inserted into something that is a plant pest. APHIS-BRS evaluates the potential to be a plant pest risk and whether it could have weedy characteristics. Through its permit and notification process, APHIS-BRS oversees importation, interstate movement, field testing, and confined cultivation. (In the case of field trials, APHIS must be notified of pending open-air tests of regulated articles). The permitting process has a 120-day review, and the streamlined notification process takes 30 days, if the product qualifies. In both cases, State concurrence is obtained before APHIS approval is granted. Sites are inspected and field data reports are required at the end of the field trial.

As the new variety nears the end of development, the developer may petition APHIS-BRS for non-regulated status, which usually happens after several years of field testing. The petition evaluations are to be completed within 180 days, but can take longer if more data are needed. An extension process exists for those products that are similar to ones that have already gone through the regulatory petition process.

Comprehensive scientific regulatory review occurs at this stage. The various steps for evaluating the applicant's petition for determination of non-regulated status include scientific review, development of a draft environmental assessment (EA), and opportunity for public comment on both the EA and the petition itself. APHIS-BRS usually requests additional data or answers, and applicants may also withdraw and resubmit applications. APHIS-BRS has never denied a petition, but 25 petitions have been withdrawn for a variety of reasons. For instance, a small company may withdraw a petition if it realizes that its product is unlikely to be successful in the marketplace.

When an evaluation is conducted, APHIS-BRS looks at the biology and genetics of the plant, the nature and origin of the genetic material used, and possible effects on other organisms in the environment or on other agricultural products. The kinds of data required in a petition include crop biology and taxonomic description, genotypic differences, phenotypic differences, field-test reports from all the releases that have been conducted under permit or notification, any relevant experimental data or publications, and any unfavorable data. To evaluate a submission, APHIS-BRS looks at

the potential for creating plant pest risk including disease and pest susceptibilities, expression of gene products, weediness, agriculture cultivation practices, effects on non-target organisms, effects on other agricultural products, and potential for gene transfer to other organisms.

Since 2000, APHIS-BRS has granted 63 petitions. A total of 98 applications were submitted and 9 are pending. Two petitions have been granted to universities - to Cornell University for a virus-resistant papaya and to the University of Saskatchewan for a herbicide-tolerant flax. Currently, the Agriculture Research Service has submitted a petition for evaluation of a plum that carries plum pox virus resistance. Since the first field test in 1987, more than 10,000 authorizations have been given at more than 39,000 sites. Each authorization for field testing can be for more than one plant line (event) and for more than one site of planting.

Whether using the permit process or the notification process, the same issues must be addressed--that the plant will be confined to the field test and that it will not persist in the environment. For notification, the field-testing confinement protocols must be available if an inspection is conducted.

APHIS-BRS field test databases include information from for-profit as well as nonprofit organizations such as academic or public institutions. Nonprofit organizations have conducted field tests of small-market (specialty) horticultural crops such as cucumber, grape, grapefruit, peppermint, melon, persimmon, petunia, and pineapple. In comparing the kinds of traits that have been evaluated by nonprofit organizations versus for-profit organizations, quite a few virus-resistant, bacteria-resistant, and fungus-resistant plants have been tested as well as a much wider variety of agronomic properties by the nonprofit sector. The for-profit sector has developed more of the herbicide-tolerant and insect-resistant traits for commodity crops. In addition, a wide range of phenotypes have been tested for product quality traits by nonprofits.

To answer the question as to whether there has been an increase or decrease in the numbers of field tests by public institutions, there has been no decrease in the number of field tests conducted by nonprofits. (The nonprofits include foundations as well as academic and public-sector institutions.) However, looking at the specialty crops, there is a dramatic decrease in the number of field tests being conducted. For example, from 1998 through 2003 the number of notifications, sites, acreage, and phenotypes for lettuce peaked in 2000; only two tests were conducted in 2003. Strawberries show the same pattern, with very small numbers of field tests being conducted and none in 2002 and 2003. Melons show the same pattern, with a lot of work being done in melons in the late 1990s but none by 2003.

In the near future, APHIS-BRS will be reviewing all aspects of its regulatory process. Although the focus of this workshop was not on regulatory changes, the information and uncertainties discussed will help APHIS-BRS clarify what must be addressed through guidance documents, in everyday communications, and in the regulatory structure.

The APHIS-BRS biotechnology Web site, www.usda.aphis.gov, offers much information on the system developed during the past 15 years. In addition, a U.S. Government Web site, www.usbiotechreg.gov, presents the approvals done by the entire U.S. government regulatory system, 'event by event,' and shows how each regulatory agency-APHIS-BRS, EPA, and FDA has evaluated each of those events that are now available for commercial production.

Assessment of Biotechnology Products: Protein Plant-incorporated Protectants

John Kough, Senior Scientist,
United States Environmental Protection Agency

The United States Environmental Protection Agency (EPA) is responsible for the assessment of biotech products that will deployed in the environment. Protein plant-incorporated protectants (PIPs), are what the EPA calls the pesticidal traits incorporated into plants. PIPs are among biotechnology-derived products that have the potential for development for specialty crops. The EPA works under laws that include the Federal Insecticide-Fungicide-Rodenticide Act for the safety of residues of pesticides that may occur on treated food. It also works under the Federal Food Drug and Cosmetic Act and a number of other acts, including the Endangered Species Act, with which all the regulatory agencies must be involved.

PIPs are defined as both a pesticidal substance and the genetic material necessary for producing that pesticide in a living plant. The genetic material is essential to the plant for it to express the pesticidal protein, but the basis of the risk assessment is the hazard of and the exposure to the pesticidal substance itself. The data the EPA uses to assess the safety of PIPs are based on the fact that these proteins have a recognizably different characteristic from conventional chemicals; for example, proteins have a predictable metabolic rate.

The EPA is part of an international effort to standardize the data requirements used to assess PIPs. One of the important characteristics is a description of the genetic material delivered to the plant, including the biology of the plant. The inheritance and stability of the introduced traits are also important, and the EPA also reviews and characterizes the expressed protein and analyzes expression levels in the plant.

Regarding dietary safety of the introduced proteins, because these proteins have been designed to control pests, they have some expressed toxicity. The required data are designed to ensure that that toxicity is specific to the target pest. This test is conducted by looking at a single, acute oral toxicity test at a very high dose—from 3 grams to 5 grams per kilogram of body weight. The test substance is pure protein, and because of the difficulty of extracting adequate amounts of material from the plant itself, the material is usually produced in an alternate organism such as a yeast or bacterium. To ensure that the material is the same as that expressed in the plant, a number of tests are conducted, including amino acid homology between the expressed protein and any possible known mammalian toxin. Food allergenicity is another issue that is especially

cogent for dietary exposure to new proteins; this area is still in the early stages of assessment in terms of scientific understanding, but the data used are based on amino acid sequence homology. The protein's stability is also examined by exposing it to intestinal fluids to determine that it breaks down rapidly, as would be expected for the majority of dietary proteins. Stability for processing is also tested, which would minimize the chances of exposure. Because of known toxicity to some environmental organisms, the tests for ecological effects review a range of surrogate species. A scientific rationale for approval could also include a demonstration of no reasonable expectation of exposure of non-target species to the toxin.

Endangered species are important to consider when looking at environmental exposure. It is difficult to address the safety issues because it is illegal to test endangered species directly. Information on related species can be used in the risk assessment, and if adverse effects are seen in that surrogate species, the next step in a risk assessment is to look at whether an exposure component must be considered. This was done for the Bt corn deployments with special concern for exposure to the Karner blue butterfly. Information from the nontarget testing and exposure that was examined for the Monarch butterfly showed no significant interaction of the Bt corn plant, especially the pollen, with the endangered species.

Decisions made by the EPA on the registration of protein PIPs focuses on making findings of reasonable certainty of no harm. The EPA depends on input from scientific peer review in the form of scientific advisory panels of experts and from public comment on rules and regulations. Some of that input comes from workshops and public meetings on issues of special focus for the EPA. The relevant EPA Web site is www.epa.gov/pesticides/biopesticides. The EPA has been especially forthcoming in presenting all the data it receives. Those data are put on the Web site, which allows the public to examine the data concurrent with EPA review. The decisions and rationales are shared openly with the public and with interest groups as the process moves forward.

FDA's Policy for Evaluating Bioegineered Foods

Mary Ditto, Consumer Safety Officer
United States Food and Drug Administration

Each of the Federal agencies involved in regulating the safety of foods in the United States, USDA, EPA, and FDA has a unique role. USDA oversees safety for cultivation, EPA oversees the safe use of pesticides, and FDA oversees the safe use and proper labeling of foods and food ingredients. In 1986 the U.S. government announced a policy, the Coordinated Framework for the regulation of products derived from the new recombinant DNA technology, or biotechnology, which stated that foods derived through biotechnology would be regulated under existing law as other foods.

FDA's statutory authority derives from the Federal Food Drug and Cosmetic Act (FFDCA). Under the FFDCA, FDA has broad authority to regulate the safety and wholesomeness of foods except meat and poultry, which is the USDA's responsibility.

Whole foods are regulated under the postmarket adulteration provision of the FFDCA. It is the legal responsibility of the producer to market safe and wholesome

foods. The FDA can act if something is not safe and can take action when something is illegal.

In 1958 Congress gave the FDA authority for premarket review of food additives. The definition of a food additive, that is anything which by its intended use is added to food, is very broad, but an exemption for premarket review was created for those additives generally recognized as safe (GRAS). Congress recognized that many substances intentionally added to food do not require a formal premarket review by FDA to assure their safety, either because their safety had been established by a long history of use in food or because of the nature of the substance and the information generally available to scientists about the substance are such that the substance simply does not raise a safety concern. Substances such as proteins, carbohydrates, and oils that are normally found in food and are normal components of food would usually fall into the category of "generally recognized as safe" (GRAS), which means they would be exempt under the food additive provisions of the law. FDA believed that many of the foods being developed with biotechnology would contain such components that are normally found in food.

Under the FFDCA, FDA is also responsible to ensure the proper labeling of foods. A food should be identified by its common or usual name. Additionally, representations made on a food label should be truthful and not misleading.

Next are described the policy and procedures that apply to bioengineered foods. The 1992 policy (Statement of Policy: Foods Derived From New Plant Varieties, May 29, 1992; 57 FR 22984) provided guidance to industry on both scientific and regulatory issues. This guidance may be used by all plant developers irregardless of the method used to develop the new plant variety. FDA evaluates the objective characteristics of the food rather than the fact that a new method was used to produce the food. New foods should be as safe as the foods that are currently on the market. The policy encourages developers to consult with FDA about new plant varieties developed using new production techniques including recombinant DNA methods.

FDA instituted consultation procedures in 1996 (revised in 1997), which clarified the interaction between the agency and developers. While the consultation process is voluntary; the requirements of the FFDCA to market safe and wholesome food is mandatory. Under the law, the requirement for premarket review for food additives may be applicable to substances "added" to a bioengineered food that do not meet the criteria for the exemption for premarket review under the GRAS provisions. Although the process of consultation is voluntary, FDA believes that the program is effective and that all bioengineered plants intended for use as food that have gone to market in the United States have been reviewed by the FDA beforehand. It is unlikely that a producer would be able to go to market without first having completed a consultation with FDA.

FDA evaluates food derived from bioengineered crops on a case-by-case basis. While there are no required set of tests that every producer must pass, every producer must evaluate the safety of their product and be able to conclude that their new variety is as safe as varieties that are currently in the marketplace. Given current technology, producers use certain tests routinely because they are the best tests to answer a particular question, but the FDA remains flexible in evaluating the information a producer provides. The discussion between the producer and the agency may be iterative. FDA will respond to a producer's submission by letter which will be posted on the agency's Internet site once a consultation is completed.

In evaluating potential safety and nutritional issues a multidisciplinary approach is taken, and a producers may expect to answer questions that address agronomic and quality characteristics; genetic, chemical, and nutritional analyses. Included is an example of the flow charts found in the 1992 policy. You will see that a producer answers a series of questions, and depending on the information about the new variety the producer may windup in the box that says "No concerns" or "consult FDA."

The safety evaluation addresses both the intended modification that has been introduced into the new variety and it also addresses potential unintended modifications that might arise as a result of the genetic engineering. In the case where the intended modification introduces a new substance into the plant (usually a protein) information about the identity and function of the introduced substance, the source of the introduced DNA, digestibility, dietary exposure and potential for altered nutrition would be presented. As to whether there may be unintended modifications a genetic analysis to show stability of the insert is helpful (usually both by segregation and molecular analysis) as well as compositional information, especially that focusing on important nutrients, antinutrients, and toxicants.

So a typical consultation would include information about the host or starting plant describing the taxonomy and identity, its history of safe uses as food, whether any harmful constituents are present in the host and any important nutrients made by the plant.

Information about the donor or source organism for the DNA would typically address taxonomy or identity, history of safe use as food, any harmful constituents, the identity and function of the introduced material (expression product). For the new variety a description of the inserted genetic material is typically presented. Additionally, the method of transformation, activity of regulatory sequences, the presence of extraneous open reading frames, the number of inserts and insertion sites, and genetic stability are discussed.

Some of the varieties that have completed consultation with the FDA include corn, cotton, canola, papaya, radicchio, flax, cantaloupe, and squash. The majority of traits that have been introduced are agronomic rather than "value-added" traits. Agronomic traits included pest resistance and herbicide tolerance. The "value-added" traits modified the oil content of seed oil plants canola and soybean.

FDA posts on the Internet a list of those products for which a consultation has been completed. The list contains summary information about the new variety that includes the name of the crop and the intended modification. FDA's letter to the producer and FDA's memo are available from this site.

There are on-going initiatives at FDA. FDA s utilizing the Biotechnology Subcommittee of the Food Advisory Committee to address questions that are pertinent to the safety of foods derived through biotechnology. The subcommittee as met to discuss allergenicity and molecular analysis. The National Academies Institute of Medicine did a report on unintended effects of genetically engineered foods on human health. The agency continues to assist in foreign capacity building in this area. We are preparing guidance to address allergenicity and the early food safety evaluation of new proteins expressed in bioengineered plants.

Additional information may be found at FDA's Internet site. Go to the Center for Food Safety and Applied Nutrition's (CFSAN) homepage (www.cfsan.fda.gov) and under "program area" choose "Biotechnology."

Panel Discussion

DR. KEITH REDENBAUGH (Seminis, Inc.): Sally, you mentioned your determinations and then adding new transformation events to those determinations. In your experience, how long has it taken to add to a determination?

DR. MCCAMMON: Up to now, the extension process has taken about as long as the original determination, but there is flexibility in the way that system was set up for us to reexamine how we use the extension process.

DR. KATHY SWORDS (Gero-Simplot Company): For John: There are some beautiful natural-resistance genes coming on the forefront that will be utilized transgenically. How does the EPA intend to regard the natural-resistance genes that may be coming from endogenous sources relative to Bts, which have familiarity?

DR. KOUGH: If it is from natural solanum-type genetic background, they would not be considered introduced genetic traits because they are part of the traditional breeding accession.

DR. JOHN STILES (Integrated Coffee Technologies): What about importation of genetically modified crops like a first importation? Would it go through the same regulatory system? Would the USDA care? If it was not going to be grown here, what would happen?

DR. MCCAMMON: The regulations are embedded in our traditional plant protection and quarantine regulations. So if it comes into the country—even if it will not be released into the environment—a permit will be needed. We are working with the North American Plant Protection Organization to determine what, if any, kind of evaluation might be needed regarding environmental exposure. If it actually is to be released in the environment, anything that comes into this country must comply with the same regulatory requirements as anything developed domestically.

DR. GREG JAFFEE (Center for Science in the Public Interest): If you look at the databases on the review process from all three agencies and you average how long it has taken to go through the review process, the average time of each of the three agencies is not egregious when you look at the data from 1992 or 1994 to 2003 or 2004. But if you break up the data around 2000 and look at the review times before 2000 and the review times after 2000, you see things take a lot longer now to go through the review process at all three agencies. Why might it be that it now takes longer to get products through the review process than it did pre-2000?

DR. KOUGH: The bottom line is that post-2000 there was a dramatic upturn in the demand for the expertise of the people who work on biotechnology related to Starlink and other issues. A limited number of people conduct these reviews, and you cannot put one person in two places at the same time. There has been an effort in all the agencies to hire more people or get contracting money to get back to the speed at which we were working before in the review process.

DR. MCCAMMON: The APHIS has added several public participation processes, which require more time. The clock does stop if we send back a deficiency letter, so it may take much longer for an applicant to address the deficiencies because

we may be asking different kinds of questions than we were earlier based on more biosafety questions coming up.

DR. JIM COOK (Washington State University): One of the genes for resistance to stem rust in barley has been cloned and transferred into barley. Would what you said in response to the question about potato apply here—that moving it in by that method would not require approval under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) other than whatever approval would be required under traditional breeding?

DR. KOUGH: The only qualifier I would add is that, because it is transformation, there are issues related to the marker gene that is used. If you just move the gene in without any foreign nonhost genetics, that would be akin to traditional breeding.

DR. KATRINA CORNISH (Yulex Corporation): I wonder if Sally would expand on something she said—that the field test, both the permits and the notifications, require State concurrence. How do you go about getting that, how much does that stall the process, and how variable is this among the States? Are there certain States where you would definitely not want to even attempt it at this point?

DR. McCAMMON: I cannot think of any reason why we would not attempt it, but I want to stress that the APHIS regulations are embedded in a long tradition of the USDA of already established work with the States in a variety of ways through our history of plant protection and quarantine work. We have good relationships with the State departments of agriculture. Developing a cooperative system regarding biotechnology was not a foreign process that we had to introduce to the States.

Whenever a field test is going to be conducted, particularly for permits, the State will get a copy of the application. We have had to work on the issue of confidential business information, and some of the States have personnel that are cleared to look at that and some States are not. For concurrence, most of the States are used to the system now so we have not had too many problems. In some States, when the issue becomes controversial, it does take a bit of time, but that is a natural result of working with one's partners.

UNIDENTIFIED QUESTIONER: What is the current status when the regulation of a native gene is changed? Does that have any different regulatory review if the promoter is changed or the expression of a gene is suppressed, or is that treated like a completely foreign gene by the three agencies?

DR. JOHN CORDTS (APHIS-BRS): Some of those discussions are still ongoing in the Agency, but most of our reviews are still very comprehensive.

DR. JIM COUGHLIN (toxicology consultant): What has happened to the January 2001 *Federal Register* notice about premarket notification?

DR. DITTO: We received more than 100,000 comments on that rule, and as we read through them and talked to our legal counsel, we realized that there are many issues about trying to require a mandatory premarket notification program on products that are whole foods. Given the number of other issues that came up after that rule was issued, the resources that were involved, and the legal questions that were raised, we have put that on hold and are proceeding under our consultation procedures. The proposal is still out there, but you have not seen much activity directly on it. However, we did make certain efforts to carry out other parts of what we said we would do in terms of increased transparency and engaging with other agencies and with the

National Academy [of Sciences (NAS)]. We have committed to finalize guidance and to produce new guidance, and those activities are ongoing.

DR. COOK: Those of us in the land grant university network are getting messages from the commodity groups that we support to go forward with the research full steam ahead but do not put it into commercial use until it is accepted in the marketplace. Do you know how many such efforts are under way? Sally showed a peak two or three years ago and now none. Are these on the shelf or have they been abandoned as projects, and do we know how many are in the pipeline and on the shelf within public-sector efforts?

DR. MCCAMMON: The ARS might have a much better idea about how to answer your question. However, generally, I think the climate now is "wait and see," and that includes academia and small business. A lot of these particular products like the squashes and the melons weredeveloped by small businesses, and those businesses have eliminated them from their portfolio and are therefore not investing any more time or money, perhaps because of the resources it takes to manage public perception and dealing with the regulatory process are beyond what a small business can withstand.

I also remember hearing that preferences change rapidly for some of these small-market crops. If it takes 3 to 5 years to get something to market from inception, the preference for that particular product may have come and gone. So you have to time your product development with the timing of market preference.

DR. KOUGH: One other thing that may account for the rising and fall off is that a number of public institutions were using technology that was proprietary and then found out that they would have trouble going forward with it.

DR. TED BATKIN (Citrus Research Board): Are you looking at the introduction of new genes? What about proteins that will downregulate genes that are moved in the plant? Do you consider those the same in the regulatory process as the addition of an external gene?

DR. KOUGH: That is a little vague. If changes would be expected to affect the nutritional quality, that would definitely need to be considered. Without more specifics on downregulation of the traits, it is difficult to answer. If you downregulated something that was known to be involved in a toxic phenomenon, like changing the glycoalkyloids in a potato plant or altering the level of ER proteins known to be related to allergens, those could need to be examined as part of the compositional analysis for the food.

DR. NEAL GUTTERSON (Mendel Biotechnology): Regarding the EPA's view of resistance genes, my understanding is basically that they regulate natural plant function. So if one were to put in a transcription factor, a kinase gene and another copy from potato back in potato, how would the EPA view that?

DR. KOUGH: Other than the possibility of something related to the regulation of that gene, it would be considered an inherent trait of that plant.

DR. CORNISH: A question for the whole panel: How far along have the regulatory rules come with distinguishing between food and farm and industrial transgenics? Transgenic tires are not quite the same thing as having a transgenic

intravenous drug, and it seems they should not have the same rigor in the rules that apply.

DR. MCCAMMON: The APHIS and the FDA have been grappling with this issue for almost 3 years. We have a joint guidance document to deal with the farm plants. We have worked with the FDA because the FDA has all the expertise and the procedures in place for evaluating pharmaceutical products, but the interface occurs from needing to decide how to treat the field test in the environment of industrial pharmaceutical products. At this point, we have put in place quite a few new field-testing requirements for growing pharmaceutical products. The APHIS has said we are not going to allow deregulation of these as they go to commercialization, so we are looking at processes for commercializing under Federal oversight as the product is being grown. Now the FDA has discussed looking at the farm as a facility.

The APHIS recently came out with an amendment to our regulation saying that if you grow an industrial-type plant product, it must adhere to the same requirements for pharmaceutical growth. All of these expand and expound on in much more elaborate detail the kinds of confinement measures that we require for growing traditional biotech products for food and feed purposes, but the main attribute of all of them is confinement. It is only an elaboration of the details of how to achieve that confinement. It is much more prescriptive for the pharmaceuticals and industrials than it is for the field testing of food products.

DR. DITTO: We talked about regulation of the final product and that joint guidance included everything pharmaceutical from animal drugs and human drugs, human biologics, animal biologics, and medical devices. From the FDA perspective, we are talking about how to produce a safe and effective product and here is a unique way to do so. We recognize that there are some unique issues. The USDA has responsibility for reviewing the confinement of field trials and changes its regulations often. One of the issues that people often do not realize is that, if people want to put the production remainders into animal feed, anything that goes into animal feed must be brought to the FDA's Center for Veterinary Medicine, which regulates animal feeds.

DR. JOHN RADIN (ARS): A gene that is available and accessible through conventional breeding procedures is far preferable because it escapes virtually all regulation, whereas if biotech procedures are used, it can be subject to a long procedure. Technologies now exist for removing foreign DNA after its usefulness is over. Would that then make the product equivalent to a conventionally bred variety?

DR. KOUGH: It is possible that would fit under conventional breeding. Since nothing like that has come forward, it is either being done currently or no one has asked our opinion.

DR. MCCAMMON: This brings up the broader issue of the baseline. What is the comparator? The 2002 NAS report began the foray into the arena that traditionally bred or nongenetically engineered plant varieties had some of these same issues. In the late 1980s and early 1990s, nobody said that these kinds of impacts would not occur with traditional breeding, but that you would use this as your comparison when you were evaluating the products of genetic engineering. Out of this came the concept of familiarity that we do have a lot of familiarity with the crop plants that are being developed and that these kinds of processes, breeding for disease and pest resistance, have occurred for the past 100 years. We have never said that significant effects are

not occurring with traditional plant varieties. If we are going to change that paradigm, it would be helpful to do so in a conscious way.

As regulations are developed and even as some of these products are being evaluated, the scientific community has to engage in an ongoing basis. Otherwise, the balance of perspectives will not occur. We will not have the benefit of your expertise and your desire to develop the kinds of things you think are beneficial.

DR. DITTO: We did put out in 1992 a document that dealt with new plant varieties and we thought that, however the new variety was derived, there are certain questions you should be prepared to answer to know whether you are bringing a safe product to market. We have depended on plant breeders who do traditional breeding to do some of that vetting, and there have been examples where some things have come to market that really were not as safe as they should have been. They were discovered and removed from the market. We must recognize that this new technology raises some unique issues related to how you could get the trait in the plant.

DR. ALAN MCHUGHEN (University of California, Riverside): Although regulatory overview looks at the product and does a reasonable job of doing so, the trigger is still process. If I am a genetic engineer and I transfer a soybean gene into a new variety of soybean, and there is nothing new and no foreign DNA, I still have to go through regulatory review and have the regulators say, "Yes, this is not new. It's okay. Go ahead." But if I did the same thing with conventional breeding, I could bypass that entirely. This is one of the problems we have fundamentally, and this has been mentioned by both of the NAS reports—in 2002 and the recent one in 2004—that the trigger is not justified scientifically. Sooner or later we will have to address that. For example, the XA21 gene going into rice is produced using both conventional and transgenic technology. Recombinant DNA technologies are virtually abandoned everywhere except China because the conventional version is a lot easier even though it is an inferior final product.

DR. THRO: There are vocal groups that are gifted in public relations that disapprove of transgenic crops because they simply disapprove of any kind of human intervention, so using a gene from the same species would not be of interest to them. That does not mean that it is not a good thing to pursue, because there are many consumers who probably would be pleased, and there are good biological reasons for doing it. But keep that wrinkle in mind.

DR. JERARDO: Organic fruits and vegetables constitute a large and growing sector of the specialty crops market. A transgenic crop is not considered organic so that part of the market might be excluded in this case.

III. Regulatory Challenges: Experiences From the Perspective of Public Researchers

Moderator: *John Radin*
National Program Leader, Plant Physiology and Cotton, ARS, USDA

The Papaya Story: Experience with Regulatory Issues

Dennis Gonsalves, Center Director,
Agricultural Research Service
United States Department of Agriculture

Hawaiian papaya is affected by papaya ringspot virus; a virus that is of worldwide importance. Work was started in 1978 to develop control measures for papaya ringspot virus in case the virus migrated into Puna district of Hawaii where 95% of Hawaii's papaya were being grown. Cross-protection work started in 1978 and the transgenic work started in 1985; in 1987 a team was assembled to push forward the transgenic work.

The new concept of pathogen-derived resistance was used. Investigators believed that transgenic papaya expressing the coat protein gene of papaya ringspot virus would be resistant to that virus. At the time, it was assumed that the coat protein gene would need to be translated.

In May 1992, 95 percent of Hawaii's papaya was being grown in Puna (53 million pounds), when the virus finally arrived. By 1994 much of the Puna papayas showed significant infection; by 1998 the yield was down by half due to the virus, and the remaining fruit was of very poor quality. By 1991, however, the research team from Cornell University , University of Hawaii, and Upjohn Company had developed a genetically engineered papaya that was resistant to papaya ringspot virus under greenhouse conditions. The transgenic line, called 55-1, was then micropropagated, and field trials were started on the island of Oahu in April 1992. Following the APHIS regulations, a 1995 field trial which was conducted in Puna on Hawaii island showed that the technology was working nicely. Using material from the first small field trial in April 1992, Dr. Richard Manshardt developed the "SunUp' and "Rainbow" cultivars that were subsequently commercialized in May 1998. The seeds were produced and released in May 1998, and in 1999 farmers began to reclaim their papaya farms. In a few years, much of Puna where the virus had been very bad several years before had been transformed into lovely papaya fields once again. The "Rainbow" papaya is now the dominant transgenic papaya grown and sold in Hawaii.

Commercialization. The application was submitted in December 1995, and by November 1996 the papaya had been deregulated by the APHIS. By August 1997 the "Rainbow" papaya was exempted by the EPA for tolerance levels. In September 1997 the FDA had completed consultations. By April 1998 the licenses to sell the genetically engineered papaya had been obtained by the Papaya Administrative Committee, a USDA Marketing Initiative. In May 1998 seeds were distributed to the growers. From 1991 when the transgenic papaya was first developed, it took about

seven years to test, deregulate, and distribute the seeds of the bioengineered papaya variety.

Funding. Much of this work was conducted using funds from special USDA grants targeted for Hawaii and the Pacific Basin islands. From 1981 to 1984 investigators received $70,000. From 1984 to 1987 investigators received $94,000. Specific funding came for this project in 1988 through 1992—about $112,000 during those 4 years.

Deregulation. Through the course of evaluating the transgenic papaya, investigators knew by genetics that there was one functional gene insert. Much of the information utilized in the deregulation application had been developed as a matter of course in characterizing the product. Investigators were asked if the transgenic papaya could be a weed; papaya had been grown for 100 years in Hawaii, but the virus was discovered in Hawaii in 1943. Papaya was not a weed before the virus came so it would logically not be a weed now; experiments were not needed to prove this point. As to whether the transgenic papaya would cross to other wild Carica papaya, the argument was made that papaya was originally imported into Hawaii and no wild papaya exists there. Investigators reported a positive experience with all three regulatory agencies.

Deregulation in Japan. Japan is very strict, but the regulations are very clear as to exactly what is required. Much more extensive data are required, along with border sequences and allergenicity. The Foreign Agricultural Service provided a $33,000 grant through the Hawaii Papaya Industry Association to partly support the work necessary for this submission to the Ministry of Health Labor and Welfare, which was done in April 2003. The ministry subsequently requested more information. The revised package will be submitted in 2005.

Biotechnology is the application of technology, and technology has to be timely. With the papaya work, the rationale was to solve a problem as quickly as possible and to do whatever was necessary to help the industry. Regulations change with time, public sentiment, and political pressures, but the impact of a transgenic product is affected by its timely deployment.

Regulatory Challenges: Virus-resistant Stone Fruit

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United States Department of Agriculture

In November 2000 an article appeared in *American Fruit Grower* titled, “Biotech, Fight Diseases, Stay Healthy: Looking for fruit loaded with cancer fighting agents and that ship well? Just wait a few years.” Four years later, what does the fruit industry

have to offer to fruit growers? The "Rainbow" and "Sun-Up" papayas are tremendous achievements, but that is all fruit breeders have to show growers after four years.

Fruit breeders are interested in this work because they want to make improvements in traits that would otherwise not be made via traditional breeding; disease resistance not available in the germ plasm, new colors, new flavors, and neutraceuticals, and they would like to improve traits in existing cultivars. There is tremendous potential for the fruit industry that relies on vegetatively propagated materials in high-value varieties. For example, 95 percent of pears in North America are from three varieties; changing one of those varieties—for example, making 'Bartlett' pears resistant to disease—could have a significant impact on the market relatively quickly. Almost the entire production of sour cherries is 'Montmorency', and more than 50 percent of the world's production of apples is concentrated in five varieties.

The timeline below illustrates the full extent and timeframe for activities leading to the development the gene transfer of plum pox virus resistance, including:

- Pre-project developmental work (regeneration and transformation technologies developed, isolation of the gene to be used for resistance, etc.).
- Years 1 and 2—Starting out as the breeder getting a new gene into a program. Undertaking transformations, plant regeneration, molecular analyses for gene expression, plant proliferation, plant acclimatization, and plant propagation.
- Years 2 to 5—Testing for virus resistance in the containment facility at Fort Detrick, Maryland, a USDA facility; gene expression studies; studies of the resistance mechanism.
- Years 6 to 13— Field testing by conducting multi-environment, multi-plum pox virus isolate field trials in 3 European countries where the virus is endemic; productivity and fruit quality tests, transgene expression tests, hybridization tests for transferring the resistance, and risk assessment studies.
- Results: The transgenic clone is highly resistant to plum pox virus, as tested for more than 8 years in three field tests in three different countries. The mechanism of resistance is now known and can be transferred through hybridization. Quality and productivity are so good that this plum could be a variety in its own right.
- Year 13—Deregulation and intellectual property issues are addressed. Progress in these areas to be followed by variety introduction, adoption by growers, and acceptance by consumers.

At the initiation of the project over 13 years ago a "state of the art" transformation vector to produce transgenic plants was employed. In the 13 years that it took to get a product close to market the regulatory climate has changed in terms of regulatory issues and consumer perceptions. This vector is no longer the most desirable in the sense of the marker and antibiotic resistance genes that it carries. Fruit breeders need long-term stability in the regulatory arena so that the genetic elements that they use now in their transformation work will have the greatest chance for regulatory approval a decade or more from now.

A survey of 32 stone fruit breeders worldwide found that few breeders are using or considering using transgenics. The reasons have to do with lack of consumer

acceptance, insufficient resources of money and laboratory space, insufficient knowledge of the useful genes, and legal and intellectual property constraints.

A strain on resources was evident in the course of developing plum pox virus resistant genotypes. For example, regulations require that all the prunings from the experimental trees have to be burned, and all the fruit has to be harvested and destroyed. A sentinel tree program is used to monitor gene flow. A laboratory program was necessary. Traditional breeding does not require much of a laboratory program if any. These costs that impinge on the program definitely are considered by fruit breeders as difficulties in starting out in this area. Tree fruits in particular take up a lot of land long term and require a lot of labor, so the decision to utilize transgenic technology in a tree fruit breeding project cannot be taken lightly. It is a costly and long term commitment. If the fruit breeder determines that this is the best approach, the regulatory issues must be addressed early in project development and must be an integral part of the testing program.

The current status of the plum pox virus resistance program is that initial discussions with the APHIS occurred in October 2003, more information was gathered from field testers in other countries, an application for non-regulated status was submitted in August 2004, and it looks like that process is going through and that a letter will arrive soon from the APHIS. Interactions with APHIS have been very positive. Constructive talks have set the stage for moving forward to get these varieties out to serve the industry and consumers.

In summary, here are the fundamentals of what is needed to support fruit breeders:

- A clear regulatory pathway
- A stable regulatory pathway because tree fruit breeding programs take a long time
- An economically feasible regulatory pathway
- Regulations that promote public confidence and good science
- Input from the scientific community as well as the public

Publicly funded researchers can provide information to facilitate regulatory considerations. To provide this information, publicly funded researchers need to know what information is relevant, and funding is needed to get this information, especially in the long term because of the long-term nature of tree fruit crops. Mechanisms are needed for efficient sharing of information between researchers and the regulatory community, because some of this information is not going to be published. There needs to be a way to share this information outside of the normal peer-reviewed publication process.

Regulatory Challenges: Sulfonylurea (SU)-Tolerant Flax

Alan McHughen, Biotechnologist,
University of California, Riverside

Herbicide tolerance did not originate with genetic engineering; plants have natural resistance to at least some herbicides. During 20 years in Saskatchewan, we developed a number of new varieties, including a conventionally bred new flax variety that was a somaclonal variant. That flax variety has since became a major variety that has been grown on millions of acres around the world without further regulatory oversight. The original application for it was 30 pages long; the genetically engineered version was many pages longer, 75 percent of which was immaterial to any increase in confidence in the safety of the product and was merely "jumping through hoops." A self-fulfilling vicious circle occurs because the public knows about the intense regulatory scrutiny of transgenics and thus believes if the regulators are so stringent with them, transgenics must be hazardous.

Agronomic performance is needed; farmers will not buy a transgenic product if it does not perform well, regardless of its wonderful new attributes. In addition, proximate analyses must be performed for conventional and transgenic products, anti-nutritive factors must be reviewed to make sure those factors do not escalate out of control, and the product must be genetically distinct and genetically stable.

It is important to know how the new product is biologically different from the status quo, whether it carries enhanced fitness (the ecological question that portends a chance of weediness), the difference between the managed ecosystem (a farm) and an unmanaged ecosystem (everywhere else), how to control unintended spread, and the benefits of the new product. Often a new variety can be grown with fewer pesticides or with less water, or it has positive nutritional attributes; these benefits must be part of the regulatory system because evaluation of the new product must be made relative to what is being grown currently.

In an analysis of the risks associated with genetically engineered foods compared with the risks of other forms of breeding, we looked at different methods of plant breeding—different types of recombinant DNA, different forms of induced mutagenesis, and ordinary crossing. The purpose of the analysis was to predict the likelihood of getting an unintended effect, a measure of potential for hazard. Genetic engineering cannot be segregated from all other forms of plant breeding, but currently the regulatory structure does just that throughout most of the world. It is not scientifically valid to trigger regulation based on a method or a process.

Foods with novel substances or altered levels of usual compounds should be scrutinized regardless of the method of breeding. A new modified food, whether genetically engineered or not, whose composition is similar to conventional versions may need little or no safety evaluation. If a food is genetically engineered and is identical to the conventional version, it does not need any more regulation than the conventional version.

Limited resources should be directed to the things that must be known as opposed to the things that are not necessarily needed to make a safety evaluation and develop a mitigation strategy if one is necessary. For similar but nonrecombinant DNA plants—for example, Xr21 for disease resistance in rice and resistance in sulfonyl urea-resistant canola—if the genetically engineered version and the conventional version pose the same risks, they should be regulated the same way. Whether that is superficial overview or deep scrutiny, both of those plants need to be regulated the same way; that is the basis of scientifically sound regulation, and that is what the public needs to know. If the trigger for regulation is based on the method of breeding, then an objective assessment is being applied to a subjective ideological foundation.

Challenges for Biotech Applications in Ornamental Crops

David Clark, Associate Professor,
University of Florida

High-cost, intensive agriculture includes many issues, such as shipping and handling, transportation, and consumer issues. Consumers have very high expectations of ornamentals because the ultimate consumer expects an unblemished product. Petunias are the model system for use in state of the art experiments on biotechnology of floriculture crops; although they represent sales of only $200 million a year wholesale. Petunias have been engineered for several potentially valuable traits for floriculture crops, including ethylene insensitivity to increase shelf life of flowers.

A flower-specific promoter from *Arabidopsis* hooked to the isopentenyl transferase gene that makes cytokinins from *Agrobacterium tumefaciens* inserted into petunia has also been shown to result in the production of larger fruit larger and bigger flowers. Other biotech solutions for floriculture include internal growth regulators (for flowers and for turfgrass), flowers that can be produced with reduced amounts of chemicals, and leaves that stay green longer. One unintended positive side effect has been the acquisition of tolerance to the fungal pathogen Cercospora, which was uncovered while engineering plants to have leaves that stay greener longer; Cercospora will completely defoliate a normal plant, whereas the stay-green plants will contain the fungus but hold their leaves.

Floral scent can be engineered by knocking out or over-expressing genes involved in floral volatile synthesis. Ornamental crops are not subject to the same regulatory agencies as edible crops, but if humans smell the plant, does that mean that ornamental producers must adhere to additional regulations intended for crops normally consumed orally? If a single gene is knocked out, and tests show that the only result is removing one scent-related chemical, how will this be regulated? Databases of genes are currently available and are being mined, and additional genes are being engineered at the rate of about one per week in our laboratory alone. This means that there are potentially several newly available technologies, but there are still questions that linger with regard to how the end product will be regulated.

Associated with the large number of transgenic possibilities are some negative aspects of the floriculture industry that do not help with the concept of releasing new biotech floriculture crops. The genetics used across the industry are highly fragmented, and the turnover of new varieties is rapid. The average life expectancy of an ornamental cultivar on the market is 3 to 6 years. It takes 4 to 6 years to develop a biotech variety, so by the end of that development, the genetics are obsolete. This problem is amplified in ornamental crops because consumers may like one color this year but another color may be in vogue next year. The markets are small: Royalties on a new variety amount to as little as $1000-$5,000 per variety per year. This combination of challenges makes it difficult for the floriculture industry to prioritize fiscal goals with regard to biotechnology. A recent survey of some of the bigger growers around the country asked what they would like in a biotech crop; about 100 people gave about 80 different answers. Everyone wants his or her own problem solved, and it is difficult to get a consensus on what is important.

Breeders in academia have difficulty getting competitive Federal dollars for working on a floriculture crops because the small size of the crops and potentially small returns on investments make them seem insignificant. Some good researchers are doing science on some of these floriculture crops, but many are working on these crops as side projects. Industry initiatives provide about half of the support in our laboratory, and direct industry relationships provide about another half, so academic research on floriculture is highly dependent on the industry. Some recent Federal initiatives have been discussed and are being implemented, but they still only represent a small input to the overall funding available for research on floriculture biotechnology. From the business aspect, justifying research and development investments is where much of the technology is stopped in the ornamental industry, and companies with small profit margins are not prepared to handle the high hurdles and the high expectations of the regulatory process.

It is difficult to define the concept of how much value is added to an ornamental crop compared with agronomic crops. For example, calculating the value of a better smelling rose is impossible because of the subjective nature of “better smelling.” The ornamental industry is also scattered in the sense that many growers have multiple crops, so one particular crop is no more important than the other. Combined, it appears that all of these costs are on the brink of being too expensive to justify the investment, so growers in the ornamental industry are getting scared off. There will always be industry problems, and biotechnology-based solutions likewise will abound. The question for the ornamental industry is whether biotechnology will play a part.

Panel Discussion

DR. LAWRENCE KENT (Danforth Center): When you look at the costs of putting together a regulatory dossier for deregulation, a major cost element in some cases is the protein purification for feeding studies. In the case of pathogen-derived resistance strategies, one can get around that cost or not incur that cost. Is that relevant in the cases of virus-resistant products and did it hold true when you dealt with the Japanese regulatory system?

DR. GONSALVES: The U.S. regulations did not require animal feeding studies, and that was the same with Japan.

DR. SCORZA: We do not produce protein so there would not be anything to test other than perhaps the marker genes, but we have not heard about that so far.

DR. GUTTERSON: For a small company to contemplate the issues of the regulatory process is not a trivial process, and several of you have been through that process. We heard earlier this morning that it seems awfully daunting to master that. Would you do it again? Is there another solution to having academics handle the regulatory process?

DR. GONSALVES: In the land-grant universities, you look at something, and if it is worthwhile doing, then you go ahead and do it.

DR. SCORZA: In our case, we really wanted plum pox virus resistance because it is an extremely serious disease. It entered the United States and Canada a few years ago and was eradicated, but it is currently a big problem in Europe. We did not have any sources of resistance at that time, so this was the only option if we wanted to be prepared for the potential of this virus appearing, which it eventually did.

DR. MCHUGHEN: If small businesses and public institutions do not do it, who is going to serve those smaller markets? The big companies have their clientele with the big crops. It is important for those of us in the public sector to get the system working to show that there are benefits to public research and public development of new cultivars of other new food products. We have to do it, even if it is terribly frustrating. If we do not do it, the public will not benefit from this technology to the extent that it should.

DR. CLARK: I would certainly do it again. We are supposed to be the unbiased source of knowledge.

DR. FERNANDEZ: Alan, at the beginning of your talk you asserted that more scrutiny from regulatory agencies makes people nervous, because they think that products that receive such additional scrutiny require it. That is a debatable proposition at best. In any of the surveys we have conducted on that kind of question, it seems to show the opposite. The more the FDA is involved, for example, the more confidence that gives people in the end product. Do you really think that less regulation would lead to more consumer confidence?

DR. MCHUGHEN: No. What I advocate is more effective regulation. We need targeted regulation across the board. If we regulated in a targeted manner, it would probably amount to the same degree of regulation we have now, but it would be more targeted to those products that truly pose risk. That will eventually build greater public trust and confidence because we will be able to tell the public that the regulation is science-based, that we are looking at the hazards, and that we are regulating based on the hazard of a particular product regardless of how it was made. It takes time to build consumer confidence, but then the public will see the products coming through, and presuming there are no disasters, that trust will eventually develop.

DR. FREDDIE HAMMERSCHLAG (USDA): You have released and are producing two varieties of papaya. Do you expect that the resistance is going to hold up, and is there work under way to release other varieties with other mechanisms of disease resistance? Having released these papaya in Hawaii, the public has apparently

accepted them; do you think this acceptance will lead the way to other acceptances of transgenics in Hawaii?

DR. GONSALVES: Based on the mechanism, I expect the resistance to hold up because the viruses in Hawaii are generally uniform. We do have other products in the pipeline. I do not think Hawaiian people are any different from people of the mainland. My observation is that if you have something that is good and well priced, consumers will buy it. I do not think the public cares that much, and they basically trust the government. My own experience is that we have had no public loss of confidence. A lot of people make a lot of claims about the papaya contaminating organic papaya, but that is not the opinion of the general public.

DR. COOK: What is the status of regulation of coat-protein-mediated resistance as a PIP?

DR. GONSALVES: A recent meeting should result in some kind of ruling that will come out soon.

DR. SCORZA: We are going through the APHIS process, and some initial discussions in general meetings with the EPA have concluded that if no protein was produced, it may fall under a different regulation. We are waiting to see.

DR. KOUGH: There was a recent meeting, and the intent is to address the issue of exempting the viral coat-protein-mediated resistance. It is still in discussion at this point. We have had other examples of virus resistance without expression of a protein. That type of information came in before there was any understanding of interfering ribonucleic acid, and we went through the process and registered the viral replicase in potatoes with minimal data.

DR. COUGHLIN: I was at General Foods and Kraft for many years waiting for approvals on irradiated foods because the FDA decided 30 years ago to regulate the process and not regulate the finished products. Mary mentioned the magic phrase of GRAS, generally recognized as safe. I spent some time working with the International Food Biotechnology Council during the 1980s, and we did not want to see a replay of what happened to irradiated foods. Could we talk about the possibility of scientific review by academic panels that might be able to self-GRAS some of these things? GRAS is 45 years old. We could home in on the techniques used to self-GRAS other kinds of foods.

DR. MCHUGHEN: There are many opportunities with GRAS, but to apply GRAS you have to first identify something new in the product. If you have genetically engineered corn that has a novel protein in the roots, for example, the corn oil from that corn is identical in composition to conventional corn. So is it proper to call that corn oil GRAS? I do not think so because that is misleading to members of the public who may be familiar with the concept of GRAS. Where there are truly different components in the oil—for example, the high oleic soybean—that does require some regulatory oversight and a determination of safety for specific purposes.

DR. GUTTERSON: The land grant institutions have a mission and you are particularly mission-oriented people in solving problems, but I worry that the average academic is not going to want to spend the time and effort to do the regulatory work required to understand that process. Even if we solve the cost side of it, for the land

grant institutions to carry out that mission will require greater support somewhere in the institutions.

DR. GONSALVES: Until you are able to test a lot of these things in the marketplace, it is difficult to look at it from any aspect except academically.

UNIDENTIFIED QUESTIONER (University of California): I was intrigued by your comment that we need a regulatory system to support public confidence. During the recent debates in California about ordinances, a common refrain that came from activists was that the FDA regulation was only voluntary. The impression was that if the regulatory system were required, there would be a higher level of consumer confidence. What would you envision in a regulatory system that improves confidence?

DR. SCORZA: When we have regulations, we should not appear to try to get rid of regulations because they are inconvenient. We have to identify the important issues and the regulations to address these important issues, and we should not regulate issues that are not important. We have to be comfortable that what we are doing make sense and that the regulations we are using will make a safe product. It would inspire confidence if we really targeted what we want to regulate and show the reason why we want to do that.

DR. MCHUGHEN: It is also important to keep in mind that regulating simply to mollify public anxiety will actually jeopardize public confidence because mistakes will be made. The Cartagena Protocol on Biosafety, which was signed by more than 100 countries, is designed to ensure the sanctity of and promote and preserve biodiversity worldwide. This protocol was sold to the public at great cost because the public wants to preserve and promote biodiversity, but the protocol does this by regulating living modified organisms (LMOs) —what the international community calls genetically modified organisms (GMOs) —and scientifically there is no connection. Of all the damage that has been done to biodiversity in the world, none has been caused by GMOs. Eventually, when the environmental damage continues and the attacks on biodiversity continue, in spite of the implementation of the Cartagena Protocol, the public will understand that they spent a huge amount of money and other limited resources supporting this protocol, but the damage is still occurring. Public confidence in that regulatory system will plummet. We do not want to see the same thing happen here.

UNIDENTIFIED QUESTIONER: Please describe the kinds of media attention that you received on the products that you dealt with or are dealing with and how you feel about being equipped to be able to address that kind of media scrutiny.

DR. GONSALVES: You would think the papaya case was “untouchable” because of the people being helped in Thailand, but Thailand is now under ferocious attack by Greenpeace. All I can tell you now is that in Hawaii and now in Thailand, there are major attacks on this papaya.

DR. SCORZA: Within the United States, any time I talk at a public group about this plum there has never been a single negative comment. We had an interesting meeting at the APHIS last year during which we were talking, among other things, about this plum. Several environmental groups were present, and they were quite interested because they felt that this virus was a new virus in the country, an exotic disease. In fact, this new plum and use of this type of technology could stop the invasion of this

virus, such as the Dutch elm problem and the chestnut blight. The environmental groups believed that if the disease got into the wild species of prunus, it would destroy forests, bird sanctuaries, and habitat. That was something I had not thought of, so our public comments gave a new light to what we could be doing.

DR. STEVEN STRAUSS (Oregon State University): The ornamentals are in floriculture where there is almost limitless genetic diversity—hybridization, radiation, and cloning. The high-powered genetic work is very good at generating the diversity that industry wants. Some of these species do establish in the environment to some extent, although some are quite sterile and not adaptive. How would regulators consider the environmental impacts, given the incredible genetic diversity and genetic experimentation that goes on all the time in that industry?

DR. CLARK: Right now we do not have the ability. I was giving a talk at the international meeting of the American Association of Botanical Gardens and Arboreta, and someone said that approximately 60 percent of all exotic invasives in this country were brought in through botanical garden introductions. We must keep our eyes open in terms of what those people are doing, but all that genetic diversity adds layers of potential difficulties.

DR. ERIC SACHS (Monsanto): We have developed various technologies and brought them into reality as commercial products through the regulatory path, but people were concerned about how well we answered questions from public interest groups. As the technologies are brought forward and as we focus on addressing some of the regulatory hurdles, it is very important to talk about what is done by developers and in particular in the universities and other interests that are developing these technologies to address the questions that linger in the public arena.

DR. GONSALVES: As we were developing the papaya, we had "farm days." I spoke at high schools. When the papaya was released, it was a major media event. People knew what we were doing. You have to look very carefully at the kind of education you are going to give people.

DR. SCORZA: Regarding the challenges for the researcher in going through the regulatory hurdles, one of the biggest difficulties is figuring out how to get this information to the public. That is a huge challenge: You have a product, and now you want to see it accepted. An important aspect of that is partnering with the commercial interests. This issue is important because we need those partners. Who will those partners be, and who has the money to do those kinds of things?

DR. CLARK: An example with Monsanto: I give lots of talks to master gardeners with a demographic of 90 percent women. I also take groups of 7-year-olds through our greenhouses and show them transgenic plants. Some of the most positive responses I have received for biotechnology are from products like Round-Up Ready Soybeans in the Midwest. Farmers' attitudes are changing, and they do not plow their fields any more. Instead, they stick the seeds into the ground, which has the potential for reducing erosion and the flow of silt into the Mississippi River and down into the Gulf of Mexico. The Gulf of Mexico is very important for the people of Florida, and everybody asks me why they have not heard about these positive developments or seen any of these data. We must be able to publicize the positive data that people want to hear about.

DR. MCHUGHEN: As public educators, we have to be careful not to sell Monsanto's products, and overwhelmingly the products currently available in agriculture

belong to Monsanto or Dupont. We run into that criticism, and I am sometimes accused of being a front man for industry and taking money under the table. That is not fun to put up with that when I am dedicated to the public good and try to provide education. I find most people do not really want to be educated, but they want to be able to trust regulators to tell them if a product is safe. A very noisy minority, but nevertheless a minority, of people do not trust regulators and believe they are in the pockets of industry. My job is to provide information to people, whether they like the technology or the product or not.

IV. Regulatory Challenges: Viewpoints From the Perspective of Private Business Enterprises

Moderator: *Bill Goldner, National Program Leader, Small Business Innovation Research, Competitive Programs, CSREES-USDA*

Regulatory Challenges: Horticultural View

Keith Redenbaugh, Associate Director of Regulatory Affairs, Seminis Inc.

Seminis is the world's largest vegetable seed company, with sales of about $500 million a year; Seminis sells vegetable seeds in about 128 countries. This discussion uses Seminis as an example to illustrate the costly worldwide safety data requirements.

The cost of developing biotech products has not changed much in recent years, but launching a transgenic biotech product will cost between $3 million and $5 million. The cost increases as time goes on and as approvals are sought on a worldwide basis; for example, Monsanto spent about $65 million to develop its Round-Up Ready Soybean.

The EPA has never finalized its view on viral coat proteins. From sitting through the FIFRA Science Advisory Panel workshop, it appears likely that the EPA will decide to require registration, but will provide certain exemptions. In my view, this is going in the wrong direction by increasing the regulations and making it more difficult to launch biotech crops.

Almost all the fruits and vegetables and many of the ornamentals are exported to other countries, so a biotech crop cannot merely go through the U.S. regulatory agencies. The developer must also look at the regulatory entities in other countries such as Mexico, Japan, Korea, Australia, and New Zealand. Europe has a unique process that is very complicated and time consuming; Europe is once again approving food use of transgenic products and has not yet ended the moratorium on approvals for environmental release for field planting.

In 1998 Seminis had a total of 25 USDA field trial notifications. In 1999 there were 58 notifications, the peak year and the largest total number of notifications. In

2000 there were 40 notifications and much activity in new crops. In 2001 the number of notifications decreased to 20. In 2002 there were only 10 field trial notifications. This is the genetic engineering activity of the world's largest vegetable seed company. Four notifications occurred in 2003, and in 2004, there was a nonsignificant increase to seven notifications or permits. Particularly for the virus resistance and the herbicide tolerance, these traits worked quite well; if Seminis were doing plant breeding and these varieties were developed through normal breeding methods, they would all be products because the technology worked. However, because of the issues of regulatory costs and market acceptance, Seminis has shelved these valuable potential products.

For fruit and vegetable research activities, all organizations working with these crops show a peak in 1999 and a steady decrease until 2004; it has about bottomed out at about 20 notifications from a high of 120. In 2000 a lot of companies and organizations were involved in developing biotech fruits and vegetables. Almost none of these companies is working hard now at developing biotech fruits and vegetables. Some products have become commercial, such as the papaya, the sweet pepper in China, and the Seminis squash; Monsanto's insect-resistant potato was but is no longer commercial. Many organizations were working on biotech projects with sweet corn and tomato but are no longer doing so.

Unexpected issues along the way have caused problems: Horticultural crops have small acreage but huge potential liability, high regulatory costs, biodiversity issues with gene flow, coexistence with organic farmers, labeling issues, and market acceptance (which appears to be a more significant issue than consumer acceptance).

Ways in which public research agencies could help include:

- Creation of a public biotech crop trait program to help get approvals for biotech crops.
- Working on freedom-to-operate issues (as the Public Intellectual Property Resource for Agriculture is doing); a recent meeting focused on a freedom-to-operate transformation vector that could be used widely.
- Capacity building in developing countries—putting in place capacity systems that will help them commercialize, which is especially needed in African countries.

Solutions for the United States and Europe include developing fewer, but highly valuable, alleles such as consumer traits, with a focus on fresh market opportunities, and using biotech genes already commercialized in agronomic crops, such as Bt and herbicide resistance. Dr. Redenbaugh concluded his presentation by stating that the industry is not moving ahead strongly because of the problems and barriers created that have encouraged industry to scale back significantly their investment in biotech crops.

Regulatory Challenges: A Technology Company Perspective

Neal Gutterson, Chief Operating Officer,
Mendel Biotechnology, Inc.

Mendel Biotechnology is a research and development company that was one of the first plant functional genomics companies working on *Arabidopsis thaliana* in 1997. The company's overall mission is to create value through the knowledge of plant pathways and, in particular, plant transcription factor function. Mendel commercializes technologies through seed and germplasm customers with direct market access via biotech traits, through chemical companies with direct market access via chemistry, and through collaboration and research services that develop long-term value. Although the company intends to commercialize products as well, this is a longer term prospect. Mendel's basic mission was to identify plant regulatory genes, discover and patent function, and then commercialize those that appeared to have high value. This has been done in *Arabidopsis*; all *Arabidopsis* transcription factors have been characterized, an extensive database was built, patents were filed on about 1,500 transcription factors (about 80 percent of the transcription factors in *Arabidopsis*), and genes have been licensed to a number of partners.

Significant costs are associated with this regulatory framework, which does not contribute to safety, and those costs have had a significant impact on Mendel's business. When Mendel was started in 1997, the founders' vision was that in 10 years a tremendous number of different crops would be transgenic products; that is not the case. Vegetables, for example, are not an area on which Mendel focuses significant commercial attention because of the lack of likelihood of commercial development in the near term. Therefore, Mendel's primary business focuses on crops that are already transgenic such as corn, soybean, and cotton.

Dr. Gutterson's interest in event-specific regulation started at a meeting in Monterey, California, about 2½ years ago that focused on specialty crops. Much analysis has been conducted on the *Arabidopsis* and cereal genomes with respect to dynamics of genome variation evolutionarily. Event-specific regulation is an unnecessary regulatory requirement that is not scientifically valid as a contributor to safety. Genomics studies during the past five years have revealed that both within species and among species, even in different families, there is enormous diversity of gene positions without effect on safety; polyploidization lies at the heart of this, and more than 60 percent of all plants have a polyploid lineage. For example, some corn varieties are as different genetically from each other as the mouse genome is from the human genome.

The premise of event-specific regulation is the idea that insertion of a novel DNA element into a plant could alter plant biology in unexpected ways, i.e., insertional inactivation of an endogenous gene or activation of that endogenous gene, an altered expression pattern of the introduced gene or other molecular changes that in theory can have safety consequences that can be elucidated by molecular characterization. Regulations call for extensive analysis of each new event. Is this scientifically valid? And, if the answer is unclear, what additional work can be done to address that? The

regulatory agencies could get involved in funding additional work in genome characterization that would help clarify this issue.

Extensive background information with mutation as a tool for crop development suggests that mutations are not inherently an impediment for developing safe products. Genome dynamics indicate that gene location is not an important consideration for crop performance. The creation of mutations has been a long-standing practice in breeding, and there are more than 2,000 crop varieties derived from mutagenesis; so mutagenesis per se will not necessarily create a safety problem. Evidence indicates that mutations do not create problems when developing novel varieties, in a way that would justify characterization at the molecular level. Once a trait has been demonstrated, it should be sufficient to conduct additional characterization of new varieties at the phenotype level. The failure to detect problems to date, and the likelihood that most insertions through transgenesis are not problematic, is linked to the large amount of genetic redundancy in plants.

Regarding grass genome dynamics, closely related edible grass species and even cultivars within species have genomes with different gene positions for individual genes that might be considered alleles. Much of this work has been conducted in maize, rice, and sorghum. There are tremendous differences in gene context, and a noticeable lack of micro-colinearity, between homologous chromosomes in rice, sorghum, and maize. The zein regions of the maize, rice, and sorghum genomes also show significant differences.

Recommendations:

- The event-specific process should be eliminated entirely.
- There is no evidence for relevance of insertion position for a transgene in the regulatory process.
- The focus should be on phenotype, as it is for breeding. Testing once a trait has been established in a crop should be sufficient in subsequent events with that same construct in that same crop.
- There is no basis for penalizing transgenesis methodology relative to breeding methodology.
- Research funding should be directed toward analysis of genome dynamics in other crops, to further support these conclusions.

Finally, no evidence exists for a safety benefit from what today is a very expensive process of event-specific characterization. Further research would be useful to understand genome dynamics in a couple of other families; given what has been learned about the conservation of function in different plants, crop-specific as well as event-specific regulation could be reduced when similar crops are being created with the same constructs.

Regulatory and Commercial Considerations for Small-market Biotechnology-derived Crops

Terry Stone, Directory of Biotechnology and Regulatory Affairs, The Scotts Company

The future is in small market crops and they are the way to obtain consumer benefit and greater consumer acceptance. Specialty biotech crops tend to be the focus of universities, the ARS, and small startup companies; as large companies are not generally interested in small-market crops. Because they are grown on smaller acreages, there exists a greater ability to manage production at different steps along the path to the marketplace. Market risk can be reduced through approval in countries with reliable regulatory systems. Real consumer benefit may enhance public acceptance; for example, a lawn that needs to be mowed only once a month is an important use of technology that is a consumer benefit, a quality of life benefit, and an ecological benefit.

The U.S. regulatory framework is based on familiarity and history of safe use. Regulatory agencies provide oversight and guidance before and after commercialization. The Monarch butterfly issue that came with Bt corn was a good example of how post-market regulatory authority demonstrated the ability to gain additional data on the safety of Bt corn to the Monarch butterfly. Thousands of field releases each year show essentially no unintended effects. Regulatory approval comes after very extensive risk assessment, scientific review, a great deal of public input, and agency decision-making. Dozens of products have been commercialized since 1996. Hopefully, the process of revision in the regulatory system will lend greater certainty to the process and enable some of these products to get to market through either the public or private sectors.

Before entering the regulatory process, universities and the ARS and other public organizations should consider the following:

- Where will the resources for product development and regulatory approval come from?
- Are the industry commodity groups and other stakeholders fully behind development and commercialization of the product?
- Are they prepared to support the product domestically and internationally?
- Are the channels understood to determine where country regulatory approvals will be needed or the product channeled from?
- Can channeling from certain markets be successfully implemented?
- Is the organization prepared to deal with media inquiries, unintentional releases, or legal challenges?

Universities and the ARS and other public organizations also should consider the following science and regulatory questions:

- Are there wild weedy relatives, threatened or endangered species, or other cumulative environmental impacts to consider?

- Are there resources to develop the molecular expression and other safety data either in-house or through a third party?
- Are there resources to develop dossiers and coordinate with oversight and other stakeholder agencies before and after regulatory approval?
- Are there resources to implement a plan to appropriately steward the product?
- Are there financial resources for a prolonged regulatory review?
- Can an economically viable product be safely commercialized considering the above?

The APHIS should establish a threshold for adventitious presence because that can greatly increase the likelihood of the product being economically viable and safely commercialized. Regulation varies tremendously from country to country. This is not just a science-based process. The extent to which the APHIS and other regulatory agencies in the United States are focusing on science is laudable, but the reality is that it is a political process, fostered in part by public interest groups who do not care about the science but have an agenda of their own. That reality affects the kinds of data, information, and ways to communicate and causes a great increase in cost that has ultimately reduced the realization and the benefits to society of the technology.

Changes in regulatory policy occur slowly. Inevitably there will be more regulatory requirements, although perhaps coupled with more flexibility. Researchers at the ARS, universities, or other public agencies should find ways to develop the data packages required to move a product through the regulatory process. A small company cannot afford to develop all of the data required to move a product through. If this can be done at a university through public funding, there is a much greater likelihood of seeing the product on the market if it is then handed off to a small company, because that is where their strength lies.

The benefits and safety of biotech crops are well documented, yet regulatory requirements are increasingly complex. Public research agencies can be leaders in ensuring a strong regulatory regime and developers and advocates of biotechnology-derived plants. This is not a private industry function; it will have to come from public institutions.

Les Pearson, Dawn Parks, Maud Hinchee
ArborGen

Perspectives on the Application of Biotechnology to Forestry

Overview: Forestry products are the third most valuable commodity after oil and gas. Trees supply the bulk of the fiber for pulp, paper, packaging and building needs. Some 5,000 products are made from trees. Three billion people depend on wood for fuel so we must harvest wood. But forests also are an essential component of our ecology. They provide wildlife habitat, help control erosion and purify water, they sustain the world's environment by emitting oxygen and sequestering carbon dioxide, and their beauty is unquestioned.

The challenge of foresters today is to maintain the natural characteristics of forests while meeting society's need for products produced from trees. It is therefore essential that our forests are managed sustainably for ourselves and future generations.

During the 20th century, wood consumption tripled around the world and continues to grow. The most practical way of preventing this increased demand from further impacting our natural forests is to increase productivity of managed tree plantations.

Silviculture is the agriculture of trees – how to grow them, how to maximize growth and return, and how to manipulate tree species compositions to meet specific objectives. Silvicultural research increased loblolly pine plantation productivity from an average of 10-20 tons per acre 40 years ago to 90 tons per acre today on the most productive sites. Advancements in site preparation and selective tree breeding have been the primary contributors to this significant increase. Biotechnology will be another important tool in the sustainable silviculture "tool kit" for stepwise improvements in productivity per acre.

As biotechnology helps to preserve natural forests, it also will give a new role to trees – roles such as pollution cleanup and restoration of threatened species. It has long been said that people who fail to see the big picture "can't see the forest for the trees." In this case, it is important that we not lose sight of trees' potential by focusing solely on the forest. By improving plantation trees, we can help sustain forests.

How biotechnology can reduce the impact on natural forests: Today, managed tree plantations provide only about one third of the world's need for wood and wood products. The rest comes from other sources, including natural forests. Clearly, if tree plantations produce more, natural forests will have to produce less. For example, in the southeast United States, loblolly pine is the major pulp species and has about a 25-year rotation. A five-year reduction in time to harvest would have a tremendous impact over time on total cellulose production per acre. Genetic research, including tree biotechnology, holds promise to produce faster-growing trees and to increase the cellulose content of individual trees.

Biotechnology can also reduce threats to tree health. Research is showing promise to introduce traits that are resistant to pests and pathogens that weaken or kill trees. Improvements through tree biotechnology may also improve weed control, enabling young trees to get a head start over nutrient-robbing weeds. Trees with these traits will improve the competitiveness of the United States forestry industry in the international market for forest products and they will improve productivity of lands intended for pulp production.

Other potential benefits of tree biotechnology: Tree biotechnology promises many other benefits beyond increased productivity. These include:

- Restoration and preservation of heritage trees. Research is under way at several institutions, including the State University of New York and the University of Georgia, to develop disease-resistant varieties of important and desirable tree species that are threatened with extinction due to diseases and pests.

Biotechnology provides the best hope to save and restore species such as American chestnut, American elm, flowering dogwood and various oak species, which have been so important to our culture and the beauty of our cities and woodlands.

- Clean-up of toxic waste and Superfund sites. It may be possible through biotechnology to develop trees capable of absorbing specific toxins from the soil. This has the potential to reduce by millions of dollars the amount of money spent on cleaning up toxic sites. The University of Georgia is among several institutions conducting research with trees for phytoremediation.
- Improvement of water quality. Just as trees can be improved to absorb toxic metals, they also can be modified to absorb excess nitrogen, which contributes to water pollution and algal bloom in waterways. Rutgers University is pioneering research in this area.
- Biofuels. The U.S. Department of Energy is researching the potential for trees to provide clean, sustainable fuels. One possibility is to convert the cellulose in wood to ethanol for use in automobile engines. Biotechnology can play a vital role in producing wood better suited for the production of ethanol, which can reduce our reliance on foreign oil.
- Improved lignin content for pulping. Biotechnology can reduce the amount of lignin in trees intended for paper manufacture. Lignin, a natural polymer found in wood, must be removed in the pulping process. Trees that have less lignin or more extractable lignin are more readily pulped, allowing mills to reduce the chemicals and energy required to remove lignin and purify cellulose (the basis for paper, packaging and many absorbent products) from wood. The mills are expected to better achieve their ambitious environmental objectives while also reducing their costs and inputs.
- Better lumber. Biotechnology may also produce straighter trees, with fewer limbs, which results in more and better lumber.

Continued research in tree biotechnology may address and solve other issues, such as why some woods resist rot and others do not or why some species are susceptible to insects and others are not. Through this continuing knowledge will come many advancements that will maximize the value and efficiency of trees.

Deregulation: Commercialization will require that biotech trees go through a regulatory process to assess risks and benefits. The framework under which the Animal and Plant Health Inspection Service (APHIS) has assessed the risks and benefits of agronomic crops such as soybean, corn and cotton is effective and protective. This is evidenced by the fact that more than 10,000 trials have been field tested since 1987 and more than 60 biotech products have entered into commerce without adverse effect on human health or the environment. This science-based approach allows for the assessment of risk on a case-by-case basis for a particular trait in a particular crop of interest. This approach is equally applicable for many of the new products under development including trees. The significant knowledge base that already exists for tree species must be considered in the regulatory process.

Many products developed in new species are likely to be produced by small companies or academia that are staffed and funded to produce the science, but are

generally unprepared for the regulatory requirements and funding to achieve regulatory approval. If regulators are able to advise companies far enough in advance on what data will likely be required, companies can focus resources and attention accordingly. Without knowing the requirements, small companies are disadvantaged and could divert valuable resources to develop data that will not be required for deregulation. Unlike large biotech companies, most small companies and academic labs do not have the luxury of a regulatory expert on staff to work through the regulatory uncertainties that could lead to delays in commercialization. In the case of trees, the significant understanding of their basic biology and management practices could obviate the need to initiate certain types of studies for biotech trees that would be redundant. In the Venture Capital or academic grant funding world of today such delays may result in lost funding, and great products could stall before they see the light of day.

The role of public research: Several institutions, including ArborGen, have made significant progress in introducing and testing genes that improve wood volume gains as well as in improving the lignin content and composition. ArborGen's trees are currently in multiple field tests to determine trait performance and to ensure overall tree performance in plantation operations. ArborGen has multiple field test sites aimed at testing trees in the geographies and environments in which industrial forestry is practiced for these species. Some of the trees currently under evaluation will be selected for further product development and future commercial sale.

Small companies are focused on the work and data to bring their product to market. Scientific familiarity about the product and the trait is learned through the scientific research, laboratory work, greenhouse experimentation and field trials that will be needed for customer acceptance as a product is brought closer to market. Small companies must rely on public research to assist with regulatory approval by developing broad scientific principles and providing baseline data. For example, in long lived species, age-to-age correlations that support early data used as predictors of performance in older trees are important for a timely product approval. While much research has focused on understanding the relationships and correlations between early ages and mature stages, more research is needed. Small companies are unlikely to be able to afford conducting this additional research, over and above what is necessary for product development, but that is required for deregulating their products. This type of data can best be generated by public institutions.

For many tree species, the potential to use backcrossing to introduce a trait into different germplasm is not practical because of self-incompatibility. Asexual propagation of elite trees will most likely be the basis for delivering high performance elite trees for plantation forestry. A single approval for multiple genotypes containing similar introduced genes, referred to as a trait by species approval, would streamline the regulatory approval process. The broad applicability of this approach would benefit small companies and academics in particular. This approach is already supported by data that demonstrates the consistent performance of transgenes across a wide range of parental genotypes, for example through the extensive crossing of transgenic annual crop species to a wide variety of different cultivars. Public research could extend the knowledge base that would be required to realize this approach.

Other areas that would benefit from public research include the development of management practices that will address potential risks and understanding how transgenic plants compare in fitness to their natural counterparts in their normal settings.

Public research could develop the foundation for decisions regarding gene flow. These decisions should be made on a case-by-case basis based on an understanding of the potential ecological impacts. For example, extensive work is under way to make the American chestnut resistant to a devastating exotic pathogen for which there is no natural resistance. In this case it seems highly desirable for pollen to flow freely to allow the spread of this trait to natural stands and promote the restoration of this species.

Summary: In summary, tree biotechnology will have many environmental and societal benefits. Faster-growing trees, developed through biotechnology, will contribute significantly to sustainable silviculture by diminishing the demand for wood harvested from old growth and natural forest stands. Many other benefits are possible, as well. These include restoration of heritage tree species such as American chestnut and American elm; clean-up of toxic wastes and nitrogen absorption; biofuels; and lignin modification to improve the production of paper. Biotechnology will help the forestry industry advance its goals of providing wood products for society while protecting the natural forests that provide beauty and essential ecological benefits. Public research will develop the baseline data and fundamental principles that allow for further development of biotech by small companies and academics. Uncertainties in the type of data required for regulatory assessment force companies to focus on those products that provide the highest potential market and return. While the technology for many products that benefit society exists, they may be significantly delayed or may never reach the market if the costs associated with deregulation are prohibitory.

Panel Discussion

UNIDENTIFIED QUESTIONER: In your realistic presentation, you talked about the costs and hurdles, and there are regulatory costs, public acceptance costs, and market acceptance costs. You hinted that you might want to elaborate more on the difference between consumer acceptance and market acceptance. You left the impression that public or market acceptance questions may be more constraining than the regulatory costs.

DR. REDENBAUGH: My observation over the years has been that consumers do not care and, at least in this country, do not have a lot of concern. If the FDA, the USDA, and the EPA have given their approval, then a product is considered fine for the consumers.

As we have tried to launch some biotech vegetable crops, the various commodity groups have said they do not want to be “next.” They think the technology is great and will solve some problems, but they do not want their product to be the next biotech “test.” Therefore, we are faced with having to lobby within the industry to convince them that these traits are going to be valuable. The problem is that most all the traits have been ones that benefit farmers, and the farmers want these traits as long as the

processors and shippers/packers will take them. The farmers would like to have these new traits because it helps them, but the shippers/packers and the processors see nothing in it for them other than trouble and problems. Until they start to see some benefits, they will be resistant. I do not see that changing until it becomes evident to them that they can benefit from the technology, which they can do if beneficial consumer traits can be so labeled. A failed example of this would be Calgene's FlavorSaver tomato, which I worked on; it benefited the consumer, and the grocery stores liked the product because they could charge more for it, so they were willing to accept it.

MR. STONE: One of the things we learned over the years is that prior to attempting to get a product into the regulatory system, we must ensure that it is wanted by the industry and that they are willing to support it all the way through the process because the trait is seriously valued.

DR. GREG CONKO (Competitive Enterprise Institute): Keith and Neal talked about the regulatory framework not being based on science that is event-specific regulation or process rather than product regulation. What, if anything, are you doing to talk to the political level opinion leaders above the regulatory establishment to create a political environment in which the regulatory agencies could feel comfortable making appropriate science-based changes?

DR. GUTTERSON: Mendel Biotechnology is a small functional genomics company, so we do not have the resources to address that political level. One of the great strengths in the United States is the confidence in the regulatory agencies. Five years ago, event-specific regulation was important because there was much we did not know, but today we do not need to do that anymore. This more technical message is best addressed at that level for a company like Mendel. Perhaps other companies can address the political agenda at a higher level.

DR. REDENBAUGH: The U.S. regulatory system is not preventing us from launching products. It is expensive and time consuming, but it is predictable and doable. If that were the only issue before us, we could be launching products without much difficulty. It is the broader worldwide requirements that we have to meet, because most of the fruits and vegetable seeds that we produce, even if they are grown only in the United States, end up in the export market; so we need to deal with all the export regulatory issues. The primary issue is market acceptance of these products, and without traits for the market or consumers, there is a real push back at this time. That is why Seminis is involved neither in lobbying at a political level to try to bring about changes within the U.S. system nor in other countries' regulatory processes.

DR. PEARSON: As a small company, ArborGen does not have the resources or the staffing to do those things, even though we realize they are extremely important.

MR. STONE: The avenues are being pursued through the Biotechnology Industry Organization and others; it is a slow process. There has to be real incentive for a decision-maker or opinion leader within the government to drive a particular agency to do something they are not already doing or are not determined to do. For example, establishing thresholds is really important and has been going on for a number of years. Our World Trade Organization case is an example of how government is trying to influence biotech acceptance, not just domestically but internationally.

DR. MCHUGHEN: Market acceptance and public acceptance are grossly overblown when we consider that anywhere in the world where consumers have been allowed access to biotech products, those products have been embraced. The primary consumer for the industry is farmers, and 85 percent of farmers have embraced this technology; that is close to saturation. I do not buy the argument that consumers do not want these biotech products; I think they do.

Through one of their subsidiaries several years ago, Monsanto had a Bt potato on the market, and I still know people who are jealously guarding their Bt potatoes and grow them every year because of the Bt capability. Monsanto should give that technology to some small company and let them run with it and take that chance. There is a market for it; maybe that market is not big enough to make money for Monsanto, but it has to be big enough to make money for a smaller company.

DR. GUTTERSON: There is no doubt that the technology has been embraced by farmers, especially in processed food crops such as soybean and maize. We had an aggressive program in transgenic strawberries, but we could not enlist Driscoll Strawberry Associates, Inc., and other major companies that are breeders to incorporate it because they had concerns about consumer acceptance. They know their market and there is definitely an issue there. If Safeway were not concerned about it, Driscoll would not be concerned about it, so it is not as simple as farmers adopting the technology.

DR. REDENBAUGH: In the case of the Bt potato from Monsanto, the reason why that was pulled from the market was because McDonald's and McCain's frozen processor said they would not accept any Bt varieties. The market was speaking. Consumers had no idea about this, but Greenpeace was out to stop it; the last thing McDonald's and other companies want is to have Greenpeace or other activists protesting. There was no benefit for McDonald's or McCain's, so they said they did not want to have it—a good example of the market pushback.

We were developing herbicide-tolerant lettuce and were working with the IR-4 Project on the registration of the herbicide on lettuce. We started running into opposition from some of the markets in the lettuce industry. They were not so sure they wanted this product and started making noise against it, and we realized it was going to be an uphill battle. If the markets do not want these products, the developers have a very difficult time launching them. That has happened to us with lettuce and with tomatoes, which has affected our development of these products.

DR. GUTTERSON: Much of it comes down to companies that protect their brands, which is a huge consumer asset. Gerber's, which was a subsidiary of Syngenta-Novartis at the time, walked away from baby foods containing transgenics. The Driscoll brand is such a prize with consumers.

DR. MCCAMMON: I would like to discuss the event-by-event evaluation and what we should do with it. The regulatory agencies want to be able to assure the public and the political powers that what the applicants bring to us or say they are doing is what they really are doing. So, if you take genes out of one background and move them into another, how do you know exactly what genetic material you have extracted and that you are putting exactly that into your recipient? That conundrum started this whole process on the molecular level. Added to that is that, with extremely powerful technologies, we get in a "fractile" mentality—How much detail should you provide to characterize what you have taken out of something? Part of the regulatory process is to

make sure that if you say you have just done a deletion or added a promoter, then that is exactly what you have done.

We have heard that it is extremely expensive just to ensure that there is only one copy and that you know exactly where that copy is located. Do you have any comments on the issue of copy number?

At what level do we start evaluating the phenotype—on morphological external characteristics or at the molecular or biochemical level?

DR. REDENBAUGH: We go way overboard in our analyses on this. I have seen thousands of transformation events and different crops that we really should be able to regulate on a gene-family-by-crop basis and not on an event basis. We do this with getting approvals of chemicals—one chemical on all the leafy vegetables, for example. We do not look at each leafy vegetable individually; we put them together and do the analysis all at once. We are going way overboard with this. We can do the same thing with genes: If you have a construct and you know what you are putting into lettuce, for example, and you put it into 20 different lettuce varieties, you should not have to go through the entire process 20 times and examine all the data 20 times. That is overkill.

The insertional mutagenesis problem is overblown. We have not seen any real problems, and if a problem did occur, we would catch and eliminate it during the breeding process.

If you look at the important nutrients in a crop, at the phenotype, and at the behavior in the field and if you do all the typical things that we have done, you will be able to catch anything. We overregulate even in the United States on this event-by-event basis, and I see no justification to continue with that sort of regulation and oversight.

DR. GUTTERSON: Regarding copy number, it is appropriate to ask whether copy number contributes to safety and what difference it makes. There are many genomes with multiple copies of genes all the time. There are complex gene families that exist in genomes. One gene more or less does not have a major impact. That level of variation exists in the edible crops we eat everyday. Five or ten years ago we did not have that background, but we do now. We know that copy number determines to some extent the level of penetrance of a phenotype. The phenotype works—that is what breeders do—and the same model should be applied to transgenics as is applied to breeding: standard practices and standard growth cycles in the field for phenotype.

DR. PEARSON: The history from the data on unintended effects is that it will not be a major contributor, so looking at the phenotype and following it through field testing needs to drive the process.

MR. STONE: It comes down to safety. If you have been able to demonstrate that your trait is safe, if the original event is fully characterized, and if subsequent events use the same trait phenotypically, you will not see anything new. The issue for industry relates to outside of the United States. At least some of the data are going to need to be generated. At the very least, there should be a confirmatory expression linking back to the original package. We should be able to notify the APHIS of this information, and in the end it should be not much different than the acknowledgment that is used for field trials today. Companies will need those data for international approvals, and the APHIS can request those additional data if they are required.

DR. DEBORAH DELMER (Rockefeller Foundation): At the Monterey meeting a few years ago, there was a suggestion that the public sector, as a group, should do one big project to try to change market acceptance. The trick would be to pick the right project. Is there any merit to that idea?

DR. REDENBAUGH: The 'Rainbow' papaya is a good example. It is a good idea, but what is really needed is something for consumers to be able to buy, handle, look at, and taste to see that it is safe and good. Seminis is interested in developing consumer products, but that is a long-term prospect for us, perhaps 10 years away from having something that is of real value to consumers. Perhaps those in the public sector have some traits that they think they could put out sooner.

UNIDENTIFIED QUESTIONER: Terry made the point that it is essential to establish contamination, gene flow, and adventitious presence guidelines. In thinking about the risks to companies of getting involved, it sounds like the lettuce growers are saying yes or no as a group; perhaps that is because they are concerned that any contamination of their seeds would cause trouble domestically and perhaps internationally. If we could agree nationally and internationally on one number for adventitious presence, would that allow niches to develop in all of these small-market crops that then perhaps would open further doors?

MR. STONE: Despite everything we are doing to be able to isolate our production and prevent seed contamination, as long as you understand the threshold or the target, you can develop a management plan to reach it. Then it comes down to a cost situation—whether you can do that at a cost that still makes your product economically viable. Assuming you can, then you can bring that product to market in those areas where you are able to financially afford to isolate it so that it will not go anywhere else. For small markets, that is probably the number one barrier to being able to move forward.

DR. REDENBAUGH: In Europe, they are working to establish these thresholds, which may be anywhere from 0.5 percent to 0.1 percent. The seed industry is saying that that level for many crops is impossible and that 5 percent is more reasonable, but it is not going to be 5 percent in Europe. The United States could benefit from this as well, although it is not quite as important for most agriculture. It will become important to have thresholds established for organic products, which currently do not have thresholds. The organic industry has thresholds for chemicals that have long been established, but they have been resistant to putting in place any thresholds for biotech components.

V.A. Approaches to Regulatory Realities: A Look into Existing Models

Moderator: June Blalock, Technology Licensing Program Coordinator, ARS, USDA

IR-4, What We Do… Provide Safe and Effective Pest Management Solutions for Specialty Crop growers

Bob Holm, National Director,
IR-4 Program, Rutgers University

The IR-4 Program's mission is to provide safe and effective pest management solutions for specialty crop growers. "Pest management solutions" encompasses chemical controls, biopesticides, biological controls, and plant biotechnology. "Specialty crops" means minor crops or small-market crops.

Specialty crops include most vegetables, fruits, nuts, herbs, spices, flowers, nursery plants, landscape plants, turf, and Christmas trees. They are high-value/low-acreage crops that make up about 40 percent of U.S. agricultural production, or $45 billion in sales. A total of 23 States derive more than 50 percent of their agricultural crop sales from "minor" crops. For example, in New Jersey, more than 90 percent of the crops grown in the State are specialty crops, and more than half of those are ornamental crop species.

The IR-4 Project is a publicly funded organization that has been around for 41 years. It exists because of the lack of economic incentive for the agrichemical industry to develop products based on small-market specialty crops. Funding comes from the USDA, the CSREES and the ARS, the land grant university system, and some commodity and crop protection industry support. This year the IR-4 budget, along with a number of other USDA programs, was cut 10 percent. The land grant system provides infrastructure support in the form of laboratories and office space. For every Federal dollar that goes into the IR-4 Project, there is a matching State dollar. The crop protection industry partners fund the out-of-pocket costs. The program also receives in-kind support in the form of analytical support, message development, and analytical supplies. The total value of the IR-4 program is $25 million to $30 million.

Field trial and residue analysis sites for the IR-4 Project are located around the country. The national headquarters is at Rutgers University, New Brunswick, NJ. The Northeast Region headquarters is at Cornell University, Geneva, NY, the North Central Region headquarters is at Michigan State University, Lansing, MI, the Western Region headquarters is at the University of California, Davis, CA and the Southern Region headquarters is at the University of Florida, in Gainesville, FL. ARS components are located around the country and headquartered in Beltsville, Maryland. The backbone of the IR-4 Project is 30 field research centers located around the country that conduct the good laboratory practices (GLP) trials that are required for the EPA to register crop protection chemicals. This system has approximately 125 full-time staff members.

The IR-4 Project is a stakeholder-driven organization that receives and acts on approximately 500 requests per year from growers, commodity groups, and the land grant university system but not from the agrichemical industry. A stakeholder workshop is held every September to prioritize requests, and about 200 stakeholders help in this task; approximately 100 projects are taken on per year, and about 700 field trials are conducted per year in the food use area. A similar amount of work is conducted in ornamentals.

IR-4 develops the protocols and runs the field trials and then conducts the analytical work and submits the registration packages to the EPA, all within 30 months or less. After that, it usually takes about 12 months to get EPA approval, and the manufacturer adds the use to the label based on the tolerances; then the crop protection tool is available for growers.

The key to IR-4 is being able to form partnerships with a number of different groups. Congress often cites the IR-4 Project as a model interdepartmental organization that works among different governmental and nongovernmental agencies. A strong partnership has been developed with the EPA and has been expanded with a technical working group in recent years. The program is experimenting with innovative approaches such as electronic submissions to the EPA, which projects about a 25 percent cost savings in doing so.

In the work plan this year, there were 49 products that the EPA is considering for registration in different classifications, and IR-4 is working with 82 percent of that total base. Working with public health products, such as mosquito control products or vector control products, is not in the program's charge; removing those four products from the total of 28 insecticides, IR-4 is working with 23 of the 24 insecticides being considered for registration this year. Prior to the Food Quality Protection Act (FQPA), IR-4 was averaging 100 clearances per year; however, in the past 4 years, the program has averaged more than 500 clearances per year, and for calendar year 2004, they expect to approach 700 clearances.

IR-4 also works with other regulatory agencies; for example, IR-4 has developed partnerships and alliances with the California Department of Pesticide Regulation during the past 4 years and has also worked with Health Canada's Pest Management Regulatory Agency (PMRA) under North American Free Trade Agreement (NAFTA). Working with Agriculture and Agrifood Canada for a few years has helped develop an IR-4 program in Canada. This partnership has greatly expanded the number of joint field trials, and some NAFTA petitions are now being reviewed by the PMRA.

Without the crop protection industry (chemical, agrichemical, and biopesticide companies) working with the IR-4 Project and providing the chemistries, IR-4 would not exist. The program alerts the crop protection industry about market potential and sharing submissions.

The IR-4 Project works with herbicide-tolerant crops. The success of RoundUp Ready Soybeans has been a curse in disguise for specialty crop growers because the crop protection industry is not developing new herbicides for broadleaf crops, which

includes most of the vegetable crops. There have been no new herbicides, and some of the older products are still on the market, despite being under regulatory concern, because many of them are B2 carcinogens.

Glufosinate-tolerant sweet corn may be the only success story. A residue program was conducted. The glufosinate gene is a marker gene for Bt so it is already in commercial corn, although it is not registered for that use. It shows good insect and weed control, but none of the processors, including Del Monte, wanted to touch the corn so it has become a niche market. A lot of Bt sweet corn is being grown in the Northeast; roadside stands are likely filled with Bt sweet corn. The IR-4 Project hopes to have registration in 2005.

The other IR-4 project is glyphosate-tolerant lettuce, a partnership among Monsanto, the IR-4 Project, and Seminis that was supposed to have been fast-track-submitted in 2001. Residue trials were conducted, but consumer-driven concerns about the product forced its cancellation. California lettuce growers can spend $500 to $1,000 an acre to hand-hoe their leafy vegetables. Consumers who buy the packaged mixes do not want to see any weeds, but there are no weeds because someone has either hand-hoed them or picked out the weeds by hand. Two shots of RoundUp will completely control all the weeds, a technology that will save the growers $400 to $500 an acre. Glyphosate-tolerant lettuce will probably sit on the shelf for a long time.

The mint industry used its money to develop a glufosinate-tolerant mint. Mint is a sterile clone that has to be vegetatively propagated, so there is no outcrossing. All parties agreed except the producer of glufosinate, Bayer Crop Science; IR-4 guidelines state that if the manufacturer will not put the use on the label, IR-4 will not do the work. This success story is not wanting from a marketing or consumer consumption standpoint, but Bayer Crop Science was concerned about the consumer liability issues.

Transgenic minor crops have potential, but it is unknown whether herbicide tolerance and insect disease resistance will actually be valuable in the marketplace.

The Orphan Drug Program at FDA

Sarah Linde-Feucht, Medical Reviewer,
Orphan Drug Program, FDA

The Orphan Drug Program focuses on developing products that demonstrate promise for the diagnosis and treatment of patients with rare diseases or conditions. Its three main functions are administering the Orphan Drug Act, a grants program, and the humanitarian use device designation program. The Orphan Drug Program is organizationally independent from the Product Review Division and interacts with all the review divisions within the FDA. Organizationally, the Orphan Drug Program is located within the Office of the Commissioner, so it acts as a mediator, facilitator, and diplomat to help the sponsors and researchers of these drugs navigate the regulatory process.

An orphan product is a drug, biologic, device, or medical food that is used in the diagnosis and treatment of patients with rare diseases. Rare diseases are defined as

those that affect fewer than 200,000 people in the United States; products are called orphans because they are not developed by the pharmaceutical and medical device industries because of economic and regulatory barriers. There is poor return on investment because the product would be used in only a small population, thus making it unattractive to the big pharmaceutical companies to invest in research and development to bring that product to market.

Researchers face significant obstacles in clinical trials for orphan diseases. Sometimes the trials do not fit the gold standard of the randomized, double-blind, placebo-controlled trial that is preferred in patients before going through the approval process; researchers may have to use historical controls or other unconventional clinical trial designs. Because the diseases are rare, the total number of patients that can be expected to enroll in a clinical trial may be too small to power the study to obtain meaningful data. The Orphan Drug Program works with researchers and with the FDA's Product Review Division to help construct these clinical trials to obtain meaningful data, although likely not in an optimal number of patients. Other challenges include the small patient population that is likely to be spread out over a large geographic area, the heterogeneity of the disease, the likelihood that few clinical experts in these diseases exist, and problems in acquiring the product and ensuring manufacturing consistency. In addition, a small company that may take on an orphan drug or medical device may be faced with not only limited resources but also limited experience in dealing with the regulatory process.

Before the Orphan Drug Act, fewer than 15 drugs were approved for rare diseases, resulting in patients with these diseases having few treatment options. Sometimes drugs used to treat other diseases were used off label for patients with rare diseases, but data to evaluate efficacy were not available for those off-label uses. In 1983 the Orphan Drug Act was passed, creating incentives for orphan drug development. The original intent of the act was to study some of these drugs for use in rare diseases. Tax credits for clinical research were believed to be the greatest incentive that could be provided to researchers and industry to encourage the study of these drugs. The tax credit is 50 percent of the clinical research costs, which is a significant incentive that can be used for 3 years back and 20 years forward, creating a valuable commodity for companies that get sold to another company in later years. Other incentives built into the Orphan Drug Act include 7 years of marketing exclusivity from the date of approval, marketing application fee waivers, grants for research, and assistance from the Orphan Drug Program.

Exclusivity. Once an orphan drug receives approval from the FDA to go on the market, the company has 7 years of marketing exclusivity, which offers some additional protection compared with patents. For example, a use patent on a product may protect it for 20 years, but it may take 15 years to bring that product to market, leaving only 5 years on the patent. If the product has received orphan drug designation, the company has 7 years of marketing exclusivity, another 2 years of protection. In the case of patent protection, the person holding the patent is responsible for defending the integrity of the patent; under the marketing exclusivity available through the Orphan Drug Act, the Secretary of Health [Department of Health and Human Services] will not approve another drug for this orphan indication during those 7 years. One other benefit of the

Orphan Drug Act exclusivity is that products that are considered unpatentable are now protected, for example certain biologic products like gene therapy, blood, and drug products whose development time is long.

Prescription Drug User Fee Act (PDUFA) fee waiver. Having an application reviewed by the FDA for marketing approval requires a significant financial investment. If an application includes clinical data, it will cost $672,000 (in FY 2005) to file an application with the FDA; if the application is for a generic drug evaluation so that clinical data are not required, the cost is $336,000. Other fees called establishment fees and product fees are paid yearly by companies to have the FDA conduct inspections. All those fees are waived if the drug is designated as an orphan drug.

Process of orphan drug designation. The application to the Orphan Drug Program must contain information about the disease, the rationale of why this drug would be useful in this disease, and an estimate of the prevalence of the disease (which must be fewer than 200,000 people). The Orphan Drug Program reviews each application, conducts some of its own research, and makes a decision based on the original application or that application plus additional requested information. Once the drug is designated as an orphan drug, it is then eligible for the aforementioned benefits.

The grants program administered by the Orphan Drug Program funds clinical research in rare diseases. The budget for the FY2004 grants program was approximately $13 million, which provides seed money for some of these researchers. Around 10 to 15 new grants are awarded each year out of the approximately 100 applications received, and the Program manages an ongoing 60 to 70 active grants at any one time. Currently, 38 products on the market have been funded in part by these grants. Much of the grant money supports improving the knowledge base in rare diseases, so even if the grant does not directly contribute to a product going to market, the advancement of knowledge in that area is a success of the program.

Twenty years after the Orphan Drug Act passed, 256 drugs and biologics have been approved for rare diseases (compared with 15 before the Orphan Drug Act). More than 1,600 drugs and biologics hold orphan drug designation; although those have not come to market yet, they may be in the pipeline or may have advanced the knowledge and in some ways the treatment of rare diseases. In addition, the growth of the biotech industry in part may be related to the Orphan Drug Act—nearly 50 percent of all biologic products that have been approved are orphan products; Genentech, AmGen, and Genzyme are examples of companies whose first approvals were orphan products. Orphan Medical is a company whose sole reason for existing is the development of orphan products.

The Orphan Drug Program is effective because of the financial and economic incentives, the marketing exclusivity, fee waivers, tax credits and grants, the regulatory assistance that the office provides, and the “status of status”—development of these orphan products is assisted because sponsors and researchers can get inside the FDA and know that they have an office that can advocate for them.

V.B. Approaches to Regulatory Realities: Exploration of Possible New Models

Moderator: *June Blalock, Technology Licensing Program Coordinator, ARS-USDA*

Biotech Crop Trait Program: A Proposal to Establish a Public Biotech Crop Trait Program (BCTP) to Assist in Regulatory Approval for "Minor" Biotech Crops

Kent Bradford, Keith Redenbaugh,
Steven Strauss, David Tricoli, and Roger Wyse
(Presented by Steven Strauss, Professor, Oregon State University)

Cost associated with R&D, particularly with regulatory approvals, is an important reason that commercialization of biotechnology, especially genetically engineered crops, have been limited almost exclusively to high-acreage commodity crops. The decline in production of new biotech varieties, as enumerated by previous presenters, results in a reasonable conclusion that regulatory costs and uncertainties are at the core of that reduction. If more output crops with direct consumer benefits were on the market, consumer acceptance would increase; many of these output crops will come from small-acreage vegetable, fruit, and ornamental crops or some niches within the commodity crops.

The continuing stream of achievements in the science of crops inspires technical confidence. There is no shortage of innovation in products that are important and have significant value for consumers and the environment, but bottlenecks in the system are preventing these niche crops from getting through to the market. In addition, U.S. agriculture is under siege from imports, with major concerns from agricultural producers about how they can stay competitive with foreign products. One way to stay competitive is to have superior technology that increases the value and reduces costs. The United States leads the world in agricultural biotechnology, but if the U.S. regulatory system is so difficult to deal with, that lead in science will be meaningless. It would be a shame not to be able to use this new technology to help U.S. farmers compete in world markets.

Some kind of public-private partnership is needed. The IR-4 Project boasts an incredible success record for registration of pesticides for minor crops; perhaps this strategic model is relevant to the biotech problem. A viability assessment is needed. The first year of such a program in biotechnology might be a feasibility study that would include a more strategic look at the issues, how the organization might work, what it might work on, and whether there is enough here to go forward given the current environment. The second year would involve developing a business plan for how this program might operate. A feasibility study would involve talking with a lot of the key stakeholders to determine whether they believe this model can be successful and to find out whether the USDA would support it; leaders would be sought to get behind this program and champion it. The business plan would enumerate what such a program would do and not do and would include extensive discussion of liability risks, particularly

in light of the acrimony about biotechnology and the existence of lawsuits. It also would include a recommended budget level, suggestions for where the money would come from, an estimate of staffing requirements, and a listing of the crop-gene-trait targets and priorities that make sense to work on now and in the near future.

If such a program were to be implemented in biotechnology, some kind of governing body would need to meet at least annually with all the stakeholders to advise on the priority targets. Having key crop stakeholder partners is essential, which is similar to the IR-4 Project.

The incredible diversity in minor crops makes it difficult to imagine that the current regulatory scheme (event-specific regulation) could ever produce maximum value. Therefore, classes of traits encoded by genes in crops—perhaps groups of crops like the leafy vegetables—might be able to get regulatory treatment all at once; further investigation of how to group these crops is needed. Dialog with regulatory agencies will be needed. Some of the key regulatory questions would be:

- What is considered reasonable design of feeding studies that get at the critical safety information as cost effectively as possible?
- Is event-specific research needed?
- How can that question about event-specific research be answered for broad classes of crops or broad transformation methods?
- Are there certain kinds of vectors or markers that regulatory agencies might exempt to make the path to market easier and faster for future biotech products? (As a public-based effort, all this regulatory information would be publicly available.)

Regarding intellectual property, there should be strong linkages with some of the efforts that are now developing to help identify technology packages and licenses to facilitate moving forward. Outreach and communication are critical in biotechnology and must be conducted carefully and independent of the developer, actively communicating the quality of the data and why the product is believed safe based on the high-quality data. Post-commercial market surveys will enhance understanding of the value and the impact of a product. Particularly in the early years, funds would need to be found in addition to public-sector support. Specialized grant funds could be sought to support general issues such as a new transformation platform, good techniques for confinement or tracking the movement of organisms, compositional variation, a database of natural variation among conventional varieties, and the best ways to give the desired levels of expression control stability.

Much of this work would be conducted outside the biotech program through contracts, but some would be done in-house. Staffing needs would include a technical/scientific staff, and facilities would include a laboratory and offices. The budget for such a program would start at approximately $5 million a year, which is about one-fifth of the IR-4 budget. Proximity to a university with active research on minor crops would be ideal. Expected clients include university scientists and breeders.

Public-sector leadership as well as investment in an IR-4-like program could be a major effort in moving biotechnology forward, acting as a critical bridge among scientific advances (which continue to be impressive), application, and public acceptance for many crops.

Models for Regulatory Relief

Carole Cramer, Gary Lemme, Steven Pueppke, Jeff Wolt
(Presented by Jeff Wolt, Professor, Iowa State University)

Big-market biotechnology has been quite successful in commercialization of input traits and this experience serves as a model for understanding regulatory hurdles and costs. This experience shows regulatory costs rise through time with any new technology as the regulatory process matures. For the example of input traits, the controversies about the Monarch butterfly and Bt corn and the Starlink episode increased regulatory costs markedly as public interest and concern were raised and regulatory scrutiny increased. Regulatory costs internationally also must be figured in, because near-simultaneous regulatory clearances for the import of these products into other countries must be in place for a product to be considered viable and marketable. Whether this is true for small-market innovations is not yet settled, so the question of international regulatory clearance may need special consideration for specific small-market concepts that may come forward.

The costs for registrations include costs for science-driven processes such as molecular characterization data, protein characterization data, and efficacy and safety testing. Related to those processes are regulatory fees, regulatory management to obtain clearances, and management costs associated with issues of regulation and marketing outside the United States. Experienced regulatory managers who have dealt with big-market products ranked the gross categories of costs using the example of a single-trait Bt registration. Their analysis shows that for a first-time registration, costs are incurred in the order (largest to smallest): outside-U.S. issues management, safety testing, regulatory management, regulatory fees, protein characterization, molecular characterization, and efficacy testing. This ranking does not change markedly with a bridging data package, other than for reduced regulatory fees.

As models for regulatory relief are considered for the small market, public-sector scientists need to expand their considerations from research activities (which remain important) to recognition of the additional importance of regulatory and issues management activities. The lesson of big-market biotechnology is that success occurs largely through emphasis on these extra-scientific issues and activities.

A number of tactics can be utilized within the public sector that can lead to an improved regulatory process and improved success in regulatory clearances for the small market:

- Streamline the knowledge of what is required for regulatory decisions versus what is "nice to know." This involves standardizing the regulatory process to the maximum extent possible, while still recognizing the desire to maintain case-by-case flexibility. The goal of streamlining is to decrease the costs incurred in developing and reviewing duplicative data.
- Develop a network of laboratories within the public sector, somewhat analogous to the network of research conducted through IR-4 but centered on the needs for the product and molecular characterization and efficacy testing that are needed for regulatory clearance of small market opportunities.
- Leverage the regulatory knowledge across the public sector so that public sector specialist in biotechnology regulation can be developed.
- Create a baseline of knowledge for understanding the process of data package development for small market products.
- Pursue products that have a clearly evident public need so as to better empower regulatory action.
- Engage nongovernmental organization as allies in development of small market opportunities that serve the public good.

When the regulatory managers were asked what they considered the most important public sector activities needed to streamline the regulatory process and making it more effective, they noted the following possibilities:

- Develop the necessary data and justification for using tiered data package development. Recognition of the level of information needed by regulators should be based on the risks and benefits posed by the opportunity. Such a tiered approach could eliminate unnecessary and expensive data requirements while maintaining those that are necessary and should be maintained.
- Participate more actively in government efforts to harmonize regulations. Harmonization takes many years to accomplish, but aggressive and consistent participation can result in lowering some of the barriers that exist throughout the world.
- Continue conducting basic studies. For developers of the technologies, the same type of basic questions arise over and over again. These basic questions should be answered in the public sector and laid to rest.
- Develop data and approaches that allow for predictable requirements.

As a model of success, the IR-4 Project could be emulated for specialty crops. Its diverse funding sources include both public and private-sector funding. The activities and administration of IR-4 are disbursed across regions, which helps in effective coordination of research. IR-4 depends heavily on its administrative advisors and on the Commodity Liaison Committee for leadership. The unique features of IR-4 that might be emulated for biotechnology are the administrative structure, the diverse base of support for funding and resources, the unique mix of dispersed and regionally focused activities (so not everything is vested in one laboratory in one region), and commodity group leadership.

Commodity group leadership will be especially important. It allows bridging of the users of the technology with the IR-4 membership, maintains focus and direction, allows for clear communication with commodity groups, and garners the support needed for championing funding and continued budget support.

A poll of regulatory managers provided examples of practical actions that the public sector could take to support small-market crops. They suggested that basic research questions should be answered that would produce data on, for example, pollen flow, gene flow, adventitious presence, digestibility tests, and insect resistance management. Also helpful would be to define when multiyear monitoring for non-target impacts might be appropriate, and the important end points in such an assessment. Justification should be created for tiered data requirements that eliminate duplicative data.

Suggestions to consider for establishing regulatory relief for small markets include:

- Continue to advance science-based understanding to gain global acceptance. Small markets are not likely to be confined to the United States.
- Generate and disseminate science to address broadly impacting issues.
- Support streamlined systems of regulation that, for a given product, differentiate through a tiered system the knowledge needed to gain regulatory clearances versus what would be nice to know from a science-based standpoint.
- Using a national model, develop regional and national networks for sharing expertise in data development and regulatory expertise.

Panel Discussion

DR. REDENBAUGH: Regarding orphan drugs, do you have situations in which a developer of a drug does not have an interest in its use for orphan purposes, and so another party comes along that wants to use that drug? If yes, how do you deal with intellectual property issues and liability? Does the original developer of that drug face liability issues when it comes to an orphan drug use by another manufacturer?

DR. LINDE-FREUCHT: Our office does not deal directly with intellectual property issues or liability issues, but here is an example. Sometimes our researchers are using a commercially available product to study the product for an orphan disease, and they may apply for the orphan drug designation. They can go to the company with the orphan drug designation and say, "The FDA thinks what we're doing is important. Maybe you do want to consider changing the label." This is what we mean by "the status of status." But the original company certainly does not have to do it if it is not in their plan. If the researcher can prove through clinical trials and through the data that this drug will work in an orphan disease, even if the label does not get changed on that drug it is still helpful to the rare disease patient group because the drug can be used off label through the practice of medicine. If the drug is then used in a patient with a rare disease and a bad outcome occurs, the original manufacturer of that drug is not

necessarily held liable. The doctor who used it off label might be liable, depending on the circumstances.

DR. COOK: Bob made an important point about the pipeline not being full anymore with respect to herbicides for the control of broadleaf weeds and, for example, horticultural and minor crops. That is just as true for the small grains such as wheat and barley. In the Pacific Northwest we are counting solely on two chemistries—the ALS inhibitors and the ACCase inhibitors. This is very serious and puts a sense of urgency into what we are talking about. What about the insecticides? Is it true there as well that new chemistries are not coming into the pipeline because of what has happened with Bt cotton and Bt corn?

DR. HOLM: No. We have been very fortunate since the FQPA because the initial focus was on the organophosphates and carbamates, which are insecticides, and then the focus was on two classes of carcinogens that include a number of herbicides and fungicides. We have worked with a wealth of new chemistries in the area of insecticides and fungicides, and this year we have seen 15 new products from companies we are working with; all but two of them are herbicides. The good news is that there are other products in the pipeline that are insecticides and fungicides; the bad news is that the herbicide discovery effort has been dramatically decreased.

DR. GUTTERSON: Regarding the IR-4 models, Steve commented that this program should not be seen as an overall advocate for biotechnology. That raises a problem, because if the government is going to subsidize this activity, it has to be assumed that a public good is associated with it. How do we navigate that challenge?

DR. STRAUSS: That requires a lot more thought and consideration. Such a program would need to be an advocate for biotechnology in the general sense, but for specific products and whether they are the best alternative, we would need to be careful not to look like a for-profit company trying to develop a product.

DR. RADIN: We already have programs in place for the public sector to conduct research and biotech risk assessment. There is a competitive grants program funding of $3 million, and the ARS has been somewhat successful in getting funds for its in-house research. Depending on how they are counted, those funds can be anywhere from $6 million to $29 million. Some of this money is encumbered, but we need a strategy to make it as effective as possible. Are you suggesting we should look at our existing funding programs and start immediately to deal with the questions in the way you are advocating? Or are you looking at new funding so that these programs can continue to do what they have been doing?

DR. STRAUSS: We are looking at new funding. For one, the biotech risk assessment program is very small considering the number of issues and crops involved. Second, there is a powerful attraction to things that are in significant commercial use now to produce the biggest impact for the research. Small-market crops are just trying to get to market and have an effect. The ARS programs are a little more pre-product oriented and more science development than partnering to release new varieties and dealing with the regulatory issues and science. It is a distinct niche for those reasons and, therefore, needs distinct funding.

DR. WOLT: The programs we have in the area of biotech risk assessment are quite oversubscribed; there is more demand for research than there are funds available. Therefore, redirecting available funding would not be appropriate for what Steve has outlined here today. We need to recognize that the types of research needed for any model we adopt will have to focus on the regulatory science, which is a different nature of science than the types of science that are funded through currently existing programs. It will need a different model and different funding sources.

DR. REDENBAUGH: Does IR-4 shoulder any liability in terms of the products that are registered? Have you ever been sued by someone who did not use the product right or had problems?

DR. HOLM: No and no. We do not even start discussing a product unless we run it by the crop protection companies and they express interest. We submit the information, but we are not the registrant on it; the company holds the liability and all the product information. If the company puts the use on the label, they retain the associated liability.

DR. COUGHLIN: Instead of modeling the IR-4, could expertise be added to the existing IR-4 centers to do biotech crops? There is expertise on each of those four campuses, and if there were four small, minor biotech centers that were extensions of what is already there, might that work?

DR. HOLM: It could work. We debated this within IR-4 and at the Pew conference this summer. There is a fairly strong feeling among many of our stakeholders that we should not get involved in expansion because of the potential frailties of the backlash from either the consumer or political systems. We do not want to jeopardize our current funding; people have actually threatened me that if we get into this program, our base funding could be threatened. We do a great service for the U.S. public by helping provide a safe and effective food supply, and we do not want to jeopardize that. We are willing and able to help serve as a model and to advise. We could even do some contract analytical work because we have the capability. There are a lot of other university systems that are capable of doing that, too.

DR. STRAUSS: I can imagine contracting with either IR-4 or some of the laboratories for much of that work while the biotech issue settles, hopefully, over time and then reevaluate later.

DR, SHARIE FITZPATRICK (Forage Genetics International): Regarding the models of IR-4 Project and the Orphan Drug Program, much of the original costs have already been borne by the primary use. When we develop models for programs, we should be aware that the budgets that have been suggested by the speakers today need to be increased, because these traits may be appropriate only in these small-market crops. They may not have been cost-shared by larger uses. What levels of funding may need to be brought to bear because of the uniqueness of these traits?

DR. LINDE-FEUCHT: Some of the products whose development we promote are add-on indications to something that is already on the market, but there are also a lot of novel compounds that are brought to market that go through without being add-ons but with orphan drug designation. A comment was made earlier about the importance of finding the balance among the challenges, but you have to balance the

cost of holding these products to the same scientific standards with the cost of doing nothing.

DR. HOLM: The cost to do an average residue study is about $100,000 and with the fee waiver from the EPA, it is about another $75,000. If you include in-kind contributions from the land grant system, it probably costs about $250,000 for us to add a tolerance or a use. We are relying on the toxicology database and refer to it from the agrichemical company that developed the use for our major market. So if the trait were specific for specialty crop markets, then the cost would be much greater.

Thirty years ago, IR-4 did one study and got one clearance; today we do one study, and our average is seven clearances. If we had to do a study on every crop, we would be working all our lives just to get through one chemical. Over the years, we have developed with the EPA a crop-grouping scheme. There are 19 crop groups with representative crops in each crop grouping. In each crop group, if we do 2 or 3 of the representative crops then we get up to 30 registrations. It makes a lot of regulatory sense because we pick the worst-case situation. With leafy vegetables, we pick spinach because the leaf will retain the most residue. The Agency does its risk assessment on the worst case, and if that holds, then everything else within that crop grouping should hold. There is an opportunity in the plant biotech area to use that same type of process, and it could be very cost effective to do so.

DR. WYSE: Have you thought about access to genes and the freedom to operate around transformation systems? We will have to bundle all of that to provide freedom to operate and that will mean bringing some of the big players on board as partners very early on.

DR. STRAUSS: That is a really big issue. A big part of the cost of the business plan would be getting serious about some of the legal issues. What it would take to get freedom to operate? Would any of the big players give freedom to operate with any of their technologies, or would they see the liability risk as being too high? For example, is Monsanto technology completely off limits for public-sector use? There may be enough in the public sector to be successful, but that would be a serious issue.

DR. MCCAMMON: The IR-4 Project is built on looking at pesticides, and if that translates into transgenic plants, there is pesticide resistance in an insect or disease resistance. But there is great potential for products that are not related to pesticides. Has anyone parsed out the costs of going through the regulatory system of food products versus pesticide products? What about the incremental costs?

DR. WOLT: We have not tried to take on this idea of trying to parse out where the costs may lie. Those costs are very inexact to begin with, and the more we try to parse them out the more uncertainty develops. The process of a Bt crop versus a small-market nonfood crop will be different, but I cannot tell you what the differences in cost might be.

DR. KEITH REDDING (Monsanto): Post-commercial or post-approval requirements also need to be considered, especially for EPA registrations and now potentially for USDA approvals, for example, IRM monitoring, surveying for resistance, and other types of data requirements. Not only will you need some group to take responsibility for it, but also there is cost in head count associated with that.

DR. WOLT: The lack of baseline information on which to base a decision for monitoring or determine an approach to monitoring is the most significant issue. Monitoring made a lot of sense on the top line, but looking at it deeper, the question comes up about just what are you trying to monitor—What type of change are you trying to see, whether it is in the food supply or in nature? This is an area that needs a lot of basic research before we encumber the regulatory process with a large variety of monitoring approaches.

DR. STRAUSS: A number of the traits that are of consumer interest are traits that result from changed regulation of genes compared with the pesticide model of having new herbicide tolerances that require complex monitoring and toxicology. It is part of the regulatory negotiation to get those changes in expression of native genes recognized as substantially equivalent or familiar, and get the product deregulated early in the research process.

DR. KENT BRADFORD (University of California-Davis): The regulations also affect the research. The discovery process is much more difficult because as soon as we want to get out in the field, we have a separate situation to deal with. We just grew three or four acres of mutagenized tomatoes in the past couple of years without any problems. We have other products that are coming through that are still in the discovery stage that are using transgenics, and we expect to have a completely different situation as far as looking at those products in the field.

DR. DELMER: A negotiation is going on with the Cartagena Protocol, and the public sector is not getting a voice in this dialog. Those who are interested should talk with Shawn Sullivan at CIMMYT, who is their intellectual property expert and has a significant interest in the public sector having a voice in this issue of liability and redress. Second, there is some need for somebody to create a list of common sense principles. For example, we have been considering nutritional improvement in sorghum, but there are some issues with gene flow in sorghum.

DR. STRAUSS: In the near term, the most important function of this public-sector entity we are starting to imagine would be to provide an effective public voice to interact with the world as well as the national regulators about what the science says and does not say. I have heard from several sources about this conspicuous absence at these critical regulatory negotiations of public-sector scientists who really know the science and technology. The activists are there, and they know the outcome they want. The public-sector scientists are poorly represented.

DR. THRO: There is a document on the document table describing an international effort to get public-sector input into the Cartagena Protocol. Pete Van der Meer from Netherlands may be spearheading that effort.

DR. GUTTERSON: Academic institutions have offices of technology transfer and their mission is to get technology out into the world. At UC you have a system-wide regulatory individual who can provide that kind of insight and support. Maybe there is a need for funding, especially for these large system-wide opportunities, for that kind of expertise being brought into the academic environment.

DR. ROUSH: I want to express skepticism that we will be able to get over these difficulties by finding traits consumers like. Zeneca produced a tomato paste in the United Kingdom (U.K.) that was inexpensive, which is the primary quality we always

hear that consumers want. They produced a tomato paste in a larger container for the same price and that was not successful. What consumers want beyond low price is often fickle. Given the 7- to 10-year timelines, how can we judge today what consumers are going to be enthusiastic about in the future? The core of people opposed to this technology is not going to be swayed by what we think consumers want. They are always going to be out there and we have to face that issue. The crops have already delivered what people wanted: They have reduced pesticide use enormously, which is something consumers have asked for since the time of Rachel Carson. If we cannot sell them on that and we cannot address these issues with that alone, we are in trouble.

DR. REDENBAUGH: Some clarification on the tomato product in the U.K. It was the best selling tomato paste in the U.K., and in 1998 Zeneca filed a request for an environmental release to grow the tomatoes in Europe. Up to that point they were growing the tomatoes in California and then processing and shipping very cheap tomato paste halfway across the world to the U.K., which was not financially profitable. In 1998 the moratorium against approvals started with a rejection of Zeneca's request to have this product approved for environmental use, so the product died because it could not grow the tomatoes locally. At that point, Zeneca decided it would let the product stay on the shelf until the supply ran out, and at that point the product disappeared. But the consumers liked the product. It was the best selling tomato paste under both the Safeway and Sainsbury brands.

DR. RADIN: Can we simplify our problems by identifying those crops with hardly any exports outside U.S. borders and focusing on those to learn how to address the issues of a society that is willing to accept these products?

DR. STRAUSS: That would be a sensible way to look at the early priorities.

DR. COOK: It is not as simple as it might seem. We have the potential for transgenic barley for resistance to root disease, but barley is grown in rotation with wheat and wheat is exported. If there is any carryover from barley in the next year's wheat crop, then there is an adventitious presence.

DR. STRAUSS: That is why we must have adventitious presence rules soon that are workable and sensible and agreed on nationally and internationally.

DR. MCCAMMON: The APHIS cannot help with the problems of adventitious presence because once we deregulate something, we are stating that it is safe. Adventitious presence has already been allowed by the regulatory system saying it is safe for its intended use. The major issues are marketing issues, especially if a genetically engineered product is mixed with a traditional or organic product. There is no line for safety as far as adventitious presence of things that have not gone through the system yet, and we cannot say it is acceptable for "a little bit" of something to get into the environment if we have not completed our environmental evaluation. It is going to be quite difficult to determine a specific threshold below which something is safe and above which it is not.

DR. JOSETTE LEWIS (US AID): Would it not be advantageous to all parties to start looking at the regulatory issues much earlier in the development of the technology, so that the burden is on the technology developers as well as the regulatory agencies to have a serious and possibly conclusive discussion much earlier? If this occurred and issues were raised, the product could be developed differently by engineering around the regulatory concerns. That means the regulatory agencies will have to be more

decisive at an earlier stage, but the technology developers also will have to go into the process much earlier. Addressing these issues earlier in the regulatory process would benefit both parties.

DR. STRAUSS: We need to use scientific wisdom. If every transgenic event, because it is transgenic, is considered an entirely unknown environmental and health risk and yet breeders can do virtually anything with conventional technology that we know will pose all kinds of risks, then this technology in specialty crops will go nowhere. The regulators need to realize that they can be a bottleneck, and they need to make some scientific decisions or the technology will not go forward.

UNIDENTIFIED QUESTIONER: The regulatory and scientific concerns are only part of the issue. The regulators are addressing the theoretical, potential concerns that have been identified around these technologies. Even after these technologies have been deregulated (by the USDA) or concerns have been addressed by other agencies, those concerns never go away in the minds of some people. As a scientific community and a regulatory community, until we stand up and clearly state when an issue is over and it is time to move on, we will continue to deal with it.

MR. STONE: The reality is that these issues do not go away. They persist. I cannot imagine a university or IR-4 taking a product all the way through and bringing it to the market and then getting international regulatory approvals as well—for a specialty or a small-market crop. It is not going to happen. There are issues that our regulators need to make decisions about and provide guidance. If you do not, our scientific community and our industry will not have a voice that will be recognized satisfactorily by the public. We understand that once Biotechnology Regulatory Services (BRS) deregulates they cannot set a threshold, but what is the BRS doing with the Agricultural Marketing Service to ensure that a threshold is being established? These are real needs and they are not being addressed in a way that is helpful to the industry.

DR. JANET WHITLEY (FDA Office of Orphan Products): The Office of Orphan Products Development and Orphan Drug Designation has a little known program called Humanitarian Use Device Regulations, which may be something to keep in mind. Humanitarian use devices are devices that have a very small market, defined as less than 4,000 people in the United States. The FDA allows the manufacturer to demonstrate safety and probable benefit, lowering a barrier to entry and reducing the regulatory hurdles. In return, the sponsors can bring their products to market. This is a tightly controlled approval process that results in approval that is not as complete as for an ordinary medical device.

VI. Breakout Discussion Group Results

On the second day of this workshop, four breakout groups were asked to brainstorm solutions to surmount challenges and identify alternative scenarios. Four issues were stated for discussion during the breakout sessions:

Issue 1. Critical (priority) crops and traits to move through the regulatory process

Summary of group responses:

Criteria for crop and trait selection:

- Ready for development
- Consumer health/nutrition
- Significant $$ Value
- Marketability/Commercial Partner
- Only biotech solution available
- Powerful market niche
- Public sector as source
- Intellectual property manageable
- Biological safety

Examples of Priority Crops and Traits:

- Fireblight resistant apple/pear
- Plum pox virus resistant plum
- Anti-oxidant blueberry
- Pierce's disease-resistant grape
- Blight-resistant chestnut
- Lignin-modified trees
- Lignin-modified forage
- Vaccines delivered through plants
- Delayed ripening bananas
- Non-allergenic peanut
- Cucurbits w/ high carotene-lycopene
- Methyl bromide replacement – strawberry/tomato
- Fungal-resistant potato

Issue 2. Areas of research that could enhance and accelerate the deregulation of small-market crops

Summary of group responses:

- Health-directed aspects of small market crops
- Research directed to consumer attitudes
- Ecological assessment of modified crops – risk/benefit
- Adventitious presence:
    - IMPACT of pollen/gene flow
    - Current level of "admixture" – tracking

    - Methods to prevent gene flow (optional use)
    - Research to promote coexistence
- Scientific meta-analysis of current products
    - to improve process for small market crops
- Research on "event-specific" regulatory issues
    - Safety of transformation process
- Allergenicity testing methods
- Baseline composition analysis – toxicological properties
- Core vector/transformation systems

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Issue 3. The appropriateness of existing models to overcome the barriers and identify new models or propose changes to existing models

Summary of group responses:

- ASSUMPTION: There is a public good associated with application of
    - biotechnology to small market crops.
- QUALITIES OF THE MODEL (based on IR-4 concept):
    - Regulatory compliance (expertise, implementation)
    - Resources/$$ - sustainable funding
    - IP support
    - Regulatory research (both science and policy)
    - Communication – safety & policy
    - Both new and previously regulated genes
    - Accelerated approvals
    - Economic incentives for partners

Issue 4. Identification of next steps

Summary of group responses:

- Build a partnership with leadership from academia and the USDA
- Develop support among Experiment Station Directors and within USDA
- Seek funds to put together teams to focus on developing a proposal and plan
- Build a constituency (e.g. commodity groups)
- Meta-analysis of regulations in light of first 10 years of experience
- Identify research objectives
- Establish a strategy for consultation with partners/industry
- Pick a set of crops and traits
- Prioritize research
- Immediately gather and analyze existing data
- Provide open access to information from both universities and the private sector
- Never give up!
- Take a strong group position. Build a new structure to bridge where we are now and where we need to go.
- Develop an organization that can act as an intermediary between the research community and the regulatory agencies (such as the IR-4 Project). It should

provide expertise as IR-4 does, and researchers should get involved early with this organization. (IR-4-like groups can propose regulatory efficiencies.)
- Educate researchers and funding organizations about needs.
- Provide seed grants to facilitate approvals.
- Develop regional or national projects within the CSREES, to support research which would pull together interdisciplinary groups and would provide a way to target/prioritize research on groups of traits, genes, and enabling technologies.

Points of consensus among the breakout groups included the development of a draft program with similarities to the USDA IR-4 Project, supporting small-market pesticide registration, and FDA's Orphan Drug Program. The proposed biotechnology program may work to facilitate the optimization of the processes required for specialty biotechnology-derived crops to meet rigorous environmental and safety reviews in the most cost-effective manner possible, thereby allowing important new specialty crop cultivars to enter the market. All four breakout groups noted that it is time for action.

Discussion uncovered a number of examples of transgenic plants sitting on the shelf. Considerable investment has been made through the use of public research and development funding to develop these shelved crops. It would be useful to compile a list of those products, since there may be a product that is ready to begin the regulatory process. Vicki Forster [Forster and Associates] will send Dr. McHughen a list of the products that have been approved; this list may be useful to the steering committee. A publication coming out in the next few months may provide this information.

VII. Recommended Next Steps

As suggested by the breakout groups:

- Form a Planning Committee to move all efforts forward. Develop a plan for the new biotechnology support program which may be based on existing models (e.g. IR-4, ODP)
- Draft white papers to assess what is known about transgenic crops and the science. A committee should be assembled to suggest white paper topics. Topics for white papers will help drive needed research. These papers should be sent to peer-reviewed journals so the international community can understand the breadth of information on which these conclusions are derived. The ongoing APHIS Safeguarding Review Committee could assist in distributing the white papers.
- Develop a research program; the data needed may be separate from the white papers, which will be more global about making the regulatory process more efficient. This research program would focus on gene composition and the collection of other relevant data to support the current regulatory system. This program will have different constituencies and practitioners than the white papers.

VIII. Actions

Workshop participants were adamant about the need for action. Consequently, two volunteer groups were organized to move efforts forward, a White Paper Development Team and a Planning Committee.

White Paper Development Team: Volunteers to develop topics for the white papers were Carole Cramer (Arkansas State University), Hector Quemada (Western Michigan University), Kent Bradford (University of California–Davis), David Williams (Chlorogen), and Neal Gutterson (Mendel Biotechnology). Dr. Gutterson will be the chair. These volunteers will communicate during the next 45 days to suggest topics for the white papers and then will circulate topic suggestions. This group is not expected to write the white papers.

Planning Committee: Planning Committee volunteers included, George Acquaah (Langston University), Ted Batkin (Citrus Research Board), June Blalock (USDA-ARS), Kent Bradford (University of California–Davis), Marvin Burns (Langston University), Michael Dobres (NovaFlora, Inc.), EPA (vacant), Bill Goldner (USDA-CSREES), Neal Gutterson (Mendel Biotechnologies), Beth Hood (Arkansas State University), Kanyan Matand (Langston University), Alan McHughen (University of California-Riverside), Sally McCammon (USDA-APHIS), Eldon Ortman (USDA-CSREES), John Radin (USDA-ARS), Nancy Ragsdale (USDA-ARS), Sujatha Sankula (NCFAP), Ann Marie Thro (USDA-CSREES), and Jeff Wolt (Iowa State University). Dr. Alan McHughen was named Chairperson of the Planning Committee.

The Planning Committee determined that the following short-term actions were needed:

- Draft an appreciation letter to the three USDA administrators who provided financial support for the Workshop. (December, 2004)
- Schedule a meeting with IR-4 Program Director, Bob Holm, to learn the nuances of the Program and determine if IR-4 model would be applicable to the issues facing regulatory consideration of specialty biotechnology-derived crops. (January, 2005)
- Interface with the White Paper Planning Group to solicit recommended white papers, as appropriate.
- Develop a plan of action to actuate the Workshop recommendations.

IX. Acknowledgements

Funding for the workshop was provided by: CSREES-USDA; ARS-USDA; Plant and Animal Systems Unit, CSREES-USDA; Competitive Programs Unit, CSREES-USDA and BRS-APHIS-USDA .

The Steering Committee expresses its gratitude to Dr. Adrienne Massey for her excellent work as Workshop Facilitator. The Steering Committee also acknowledges the important contributions of the following individuals who made the workshop a success:

Steven Strauss, Carole Cramer, Kent Bradford, Jeffrey Wolt, Gary Lemme, and Stephen Pueppke, for insightful development of potential program models as bases for discussion of the needs of specialty transgenic crops;

M. Martin, M. Duryea, M. Burns, J. Cook, E. Ortman, K. Bradford, L. Kent, for serving as the breakout group leaders;

Ted Blumenthal (NCFAP), for his support of the implementation of the Workshop;

Andrew P. Wilson and Amy Rhodes (CSREES, USDA) for their assistance in recording the Workshop discussions;

Donna R. Savage, M.Ed. and ELS, Science Writer, Intelligent Fingers, Kensington, MD.

Appendix A: Biographies

Steering Committee

June Blalock: June Blalock has been Coordinator of the Technology Licensing Program at the U.S. Department of Agriculture (USDA), Agricultural Research Service since 1993. Prior to joining USDA, she was Associate Director of the Triangle Universities Licensing Consortium (TULCO), where she had primary responsibility for licensing biotechnology and biomedical inventions. She has held sales and marketing positions at International Biotechnologies, Inc. and has taught microbiology at the University of Maryland and at Goucher College. Ms. Blalock currently serves as a member of the Expert Advisory Committee for the Central Advisory Service on Intellectual Property (CAS) of the Consultative Group on International Agricultural Research (CGIAR). She also serves on the Advisory Board for the Agricultural Biotechnology Support Project II (ABSP II) and as a member of the U.S.-India Joint Working Group on Agricultural Biotechnology. She represents USDA in negotiations related to the International Treaty on Plant Genetic Resources for Food and Agriculture (IT) and in the U.S. Government interagency working group on Access and Benefit Sharing (ABS) pursuant to the Convention on Biological Diversity (CBD). Ms. Blalock is a member of the Licensing Executives Society (LES), the Association of University Technology Managers (AUTM), and the American Society for Microbiology (ASM).

Marvin Burns: Dr. Marvin Burns received a B.S. in Agronomy from Fort Valley State University, an M.S. in Agronomy from the University of Wisconsin, and a Ph.D. in Plant Breeding and Pathology from the University of Arizona. After receiving his doctorate, Dr. Burns served as Head of the Department of Plant Science at Prairie View A&M in Texas for four years. In 1978, he moved to Tuskegee University in Alabama and served as Head of the Department of Agricultural Sciences for the next 10 years.

In 1988, Dr. Burns was a Visiting Professor at the University of Delaware and in 1989, he was a Visiting Scientist in the Discovery Group at American Cyanamid in Princeton, NJ. During both of these Visiting Professor positions, Dr. Burns learned valuable biotechnology skills and techniques that he later used to establish the first biotechnology laboratory at Tuskegee University.

In 1991, Dr. Burns embarked upon a long and illustrious international career when he became the Plant Breeder/ Pathologist with the RAV II Extension and Research Project in Zaïre (now Congo) for two years. He then moved to Cameroon where he served as the Plant Breeder/Pathologist with the Root and Fiber Crop research program for two years. Dr. Burns has also had short-term assignments in Guyana, El Salvador, Burkina Faso, Chad, Zaïre, South Africa, Nigeria, Liberia and Rwanda.

In 1995, Dr. Burns left Tuskegee University to become the Associate Administrator of Extension at Langston University. In 1997, he was named the Acting Dean for Research and Extension and in 1998 was named the Dean of the newly formed school of Agriculture and Applied Sciences, where the E (Kika) de la Garza Institute for Goat Research is now housed.

Bill Goldner: Dr. William Goldner has served as a National Program Leader for the USDA-CSREES Small Business Innovation (SBIR) Program since 1999. He is responsible for the Plant Production and Protection (Biology and Engineering) and Industrial Applications program areas. Prior to joining USDA, Dr. Goldner held positions as: an Associate Biochemist at the Hawaiian Sugar Planters' Association (now Hawaii Agricultural Research Center); a Research Scientist/Project Manager for Union Camp Corporation (a major forest products company [now part of International Paper Company]); and most recently as Technical Strategy Manager for Applied Genetics in the Biotechnology Development Group for the Global Agricultural Products Division of American Cyanamid Co. (a major crop protection company [now BASF]). While at Union Camp and American Cyanamid, he served for six years as an Associate Professor in the Graduate Program in Plant Biology at Cook College, Rutgers University.

Dr. Goldner's research background includes: plant carbohydrate biochemistry; the physiology of woody plant growth, development, and abiotic stress tolerance; plant breeding; accelerated genetic selection of forest trees and agronomic crops; forest biotechnology; and production horticulture. He has published several research articles and received two patents, including one on the production of the anti-cancer compound taxol. He is a recipient of the Union Camp Corporation *Research Creativity Award* – for work leading to implementation of technology with striking commercial significance. He holds a Ph.D. in Plant Physiology from the Pennsylvania State University.

Dan Jones: Dr. Daniel Jones is the National Program Leader for Biotechnology with the USDA Cooperative State Research, Education, and Extension Service in Washington, DC. He holds a B.S. degree in chemistry from the University of Iowa and a Ph.D. in biochemistry from the University of Michigan. He conducted postdoctoral research on protein chemistry and structure at Georgetown University in Washington, DC and at the Brookhaven National Laboratory in New York.

Dr. Jones currently directs the Biotechnology Risk Assessment Research Grants Program and the Microbial Genome Sequencing Program at USDA. He served previously as the Deputy Director of the USDA Office of Agricultural Biotechnology where he developed biotechnology research opportunity areas and priorities and provided executive secretarial support for advisory, sub-cabinet, and senior staff committees developing biotechnology policy. He also chaired several national biotechnology workshops and testified before Congress on biotechnology issues. Dr. Jones has published a number of papers on the research and regulatory aspects of biotechnology, and he has given invited presentations on federal biotechnology funding and policy options.

Ed Kaleikau: Ed Kaleikau received his Ph.D. in plant genetics from Kansas State University and was a postdoctoral research fellow in plant molecular biology at Stanford University prior to joining the U.S. Department of Agriculture in 1993. Dr. Kaleikau served as Division Director of the Plant Systems Division of the National Research Initiative (NRI) Competitive Grants Program of USDA's Cooperative State Research, Education, and Extension Service. In addition, he has served as Co-Program Director of USDA's Biotechnology Risk Assessment Research Grants Program, the NRI Agricultural Systems Program and the Initiative For Future Agriculture and Food Systems (IFAFS) Plant Genome and Bioinformatics Programs. He currently serves as National Program Leader for several NRI competitive grant programs including: the Plant Genome, Bioinformatics and Genetic Resources Program, the Plant Biosecurity Program, the Functional Genomics of Agricultural Organisms Program, the Applied Plant Genomics Program, and the joint USDA/NSF/DOE programs for the Arabidopsis, Rice and Maize Genome Sequencing Projects. Dr. Kaleikau has represented USDA on numerous National committees including the U.S. - E.C. Task Force on Biotechnology Research, the Agricultural Biotechnology Research Advisory Council, the National Genetic Resources Advisory Council, and the National Science and Technology Council's Interagency Working Group on Plant Genomes.

Kanyand Matand: Dr. Kanyand Matand is a native of the Democratic Republic of Congo in Central Africa, where he was Leader of the National Peanut Breeding Program at the Congolese National Agricultural Research and Extension Service (RAV/SENRAV), where he conducted plant breeding research at the regional, national and international levels, collaborating with the International Crops Research Institute for the Semi-Arid Tropics (ICRISAT), India, to successfully introduce improved peanut cultivars into the crop production of the Congo. In 1999, Dr. Matand received a Ph. D. in Crop Biotechnology at Alabama A & M University, Huntsville, Alabama. He is currently an Assistant Professor at Langston University, where he established the Langston University Center for Biotechnology Research and Education (CBRE), a program for which he serves as Coordinator. Current research at the CBRE focuses on tissue culture and transformation of tall wheatgrass and genomics studies of peanut and goat. The Center also focuses on the training of Oklahoma high school science teachers and students in biotechnology through workshops and weekend academies. In addition to research, Dr. Matand also teaches courses in the Department of Biology.

Sally McCammon: Dr. McCammon serves as Science Advisor in the Animal and Plant Health Inspection Service (APHIS). Currently, Dr. McCammon heads the Office of Science for the Deputy Administrator for Biotechnology Regulatory Services. In this capacity, she works to assure the appropriate scientific basis for policies, regulations, and assessment decisions in biotechnology. She has served in a variety of policy and liaison roles for biotechnology and other initiatives including as the agency liaison to the National Academy of Sciences for reports on biotechnology.

Internationally, she is the U.S. head of delegation to the Organization for Economic Cooperation and Development's (OECD) Working Group on Harmonization of Regulatory Oversight in Biotechnology (Working Group); was the alternate U. S. delegate to the Codex ad hoc Intergovernmental Task Force on Biotechnology; and has represented the United States in activities aimed at implementing the Biosafety Protocol, particularly the BioSafety Clearinghouse.

She has been involved with regulatory review and biosafety operational and policy issues and nternational biotechnology regulatory harmonization for over fifteen years and invited speaker and participant in numerous international and national meetings, workshops, and symposia. She has also testified before Congressional committees and sub-committees.

Eldon Ortman: Dr. Eldon Ortman retired in 2001 after a distinguished career as the entomology Department Head and subsequently Associate Ag Experiment Station Director at Purdue University. Dr. Ortman holds a Ph.D. in entomology from Kansas State University. Since 2001, he has held a shared faculty position at CSREES, USDA. He is a past President of the Entomological Society of America and a Fellow of the American Association for the Advancement of Science.

John Radin: Dr. John Radin is the Senior National Program Leader for the USDA Agricultural Research Service in the areas of Plant Physiology and Cotton at the Beltsville Area Research Center. He holds a Ph.D. in Plant Physiology from the University of California, Davis. Dr. Radin's research has involved water- and nutrient-use efficiency and crop responses to environmental stress, especially heat and drought. He is the author or co-author of 70+ refereed scientific research or review articles and 10 book chapters.

His current responsibilities include: Technical Staff Advisor to the Administrator of ARS; liaison to agricultural stakeholders, especially to the cotton industry; determining goals and priorities for ARS research within areas of responsibility (plant physiology, plant biotechnology and biotechnology risk assessment/risk mitigation, and cotton production and processing); and leading, coordinating, and managing research in ARS to achieve those goals.

Dr. Radin is a Fellow of the American Society of Agronomy and is also a Fellow of the Crop Science Society of America. He is a recipient of the D.R. Hoagland Award for research benefiting agriculture, presented by the American Society of Plant Physiologists (now American Society of Plant Biologists)

Sujatha Sankula: Dr. Sujatha Sankula is Director of Biotechnology Research, National Center for Food and Agricultural Policy. Sujatha Sankula joined the National Center for Food and Agricultural Policy (NCFAP) in 2001. Prior to joining NCFAP, she has held research positions at the University of Delaware and Louisiana State University where she worked on biotechnology-derived crops and their impacts on weed management and crop production practices and IPM approaches to pest management in various field crops and vegetables.

A major focus of her research program at NCFAP is to evaluate the impact of biotechnology-derived crops in the United States and elsewhere in the world. Other research activities include exploration and analysis of issues that confront biotechnology in agriculture and performance of domestic and international education and outreach to promote an open and honest dialogue between various stakeholders.

She has authored three book chapters, 15 peer-reviewed publications, and 40 abstracts and research reports. She coauthored a report on “Comparative environmental impacts of biotechnology-derived and traditional soybean, corn, and cotton crops” which was commissioned by the Council for Agricultural Science and Technology. As a recognized authority on biotechnology, Sankula has briefed the Environmental Protection Agency, U.S. House of Representatives Committee on Science and the U.S. Senate and House Agriculture Committees on the environmental impacts of crops developed through biotechnology methods. Sankula holds a Ph.D. in Weed Science from the Department of Plant Pathology and Crop Physiology at Louisiana State University

Ann Marie Thro: Dr. Thro is the National Program Leader for Plant Breeding and Genomics for the USDA - Cooperative States Research, Education, and Extension Service (CSREES). In this capacity, she works to provide leadership to focus federally-funded state research on plant breeding, genetic resources, genomics, and transgenic plants. Dr. Thro earned a Ph.D. and M.S. in plant breeding and genetics from Iowa State University, a B.S. in Agronomy from Virginia Polytechnic Institute and State University, and a B.A. in history and languages from Bryn Mawr College. Prior to joining CSREES she served as Commissioner of the USDA Plant Variety Protection Office; Coordinator of the International Cassava Biotechnology Network based at CIAT (the International Center for Tropical Agriculture) in Colombia; Assistant and Associate Professor of Agronomy at Louisiana State University, and Technical Advisory to the National Grain Legume Program in Gandajika, Zaire (now the Democratic Republic of Congo). Dr. Thro has 12 years of experience as a field plant breeder and has published 22 articles in refereed research journals. Dr. Thro’s interests include environmentally, economically, and socially sustainable agriculture, with specific reference to the contributions of plant breeding, genomics, and biotechnology.

Facilitator:

Adrianne Massey, Ph.D., Principal, A. Massey and Associates

Dr. Massey has been involved with scientific research, education, workforce training and public policy for over 20 years. Before starting her own company, she was Vice President for Education and Training at the North Carolina Biotechnology Center where she directed the Center's award-winning public education and workforce training programs from 1990-1997. She was hired by the Center in 1988 to develop and implement projects that combined science, technology development, public policy and communication. In this capacity she mediated consensus-building activities among companies, environmental organizations, government officials, public interest groups, ethicists, university administrators and scientists.

From 1982-1987 she was on the faculty of the Zoology Department at North Carolina State University where she taught and conducted research in physiological ecology and evolutionary genetics. During that time she was also an instructor for courses in tropical ecology offered by the Organization of Tropical Studies in Costa Rica and Duke University.

In addition to publishing scientific articles on her research, Dr. Massey was an invited contributor to the U.S. Congressional report, *Field Testing Genetically Engineered Organisms: Ecological and Genetic Issues*, sponsored by the Office of Technology Assessment, and to the National Academy of Sciences report, *Applied Environmental Research Opportunities*. She is co-author of the best-selling textbook on the science, applications and societal issues of biotechnology, *Recombinant DNA and Biotechnology*, published by American Society for Microbiology

(ASM) Press. Her second book for ASM Press, *Biology and Biotechnology: Science, Applications and Issues*, a textbook for undergraduate non-science majors, will be released in 2005.

Dr. Massey served as the Science Advisor for the PBS series, *BREAKTHROUGH: Television's Journal of Science and Medicine,* sponsored by Connecticut Public Television; was the original Director of the North Carolina Environmental Technology Consortium; participated in the international negotiations of the Biosafety Protocol; and has developed interactive exhibits for science and technology museums. She has served on a number of federal and state advisory panels on scientific research, education and public policy and is a frequent lecturer on the science, applications and policy issues of biotechnology.

Presenters:

Alberto Jerardo, Economist, USDA – ERS: Since 2001, Alberto Jerardo has been the floriculture and nursery crops analyst in the Specialty Crops Branch, Market and Trade Economics Division. He is responsible for the Floriculture and Nursery Crops Outlook report and yearbook. He also is the ERS analyst of U.S. agricultural imports and is responsible for the import section of *Outlook for U.S. Agricultural Trade.* Prior to his current position, Andy was co-coordinator of *U.S. Agricultural Trade Update.* He also authored the international macroeconomics section of *Outlook for U.S. Agricultural Trade* and *U.S. Agricultural Update.* Prior to joining ERS in 1989, Andy was an energy demand forecaster at the U.S. Department of Energy. Andy has a Ph.D. in Economics from the University of California, Riverside, 1982; an M.A. in Economics from the University of California, Santa Barbara, 1976, an M.S. in Quantitative Business Methods from California State University, Hayward, 1975; and a B.A. in Economics from California State University, Hayward, 1973.

John Kough, Senior Scientist, EPA: Dr. Kough is a Senior Scientist in the EPA's Office of Pesticide Program's Biopesticides and Pollution Prevention Division. Dr. Kough has been at EPA since 1990 working in the biotechnology programs in the Office of Prevention, Pesticides and Toxic Substances. In the Office of Pesticide Programs, he has reviewed the scientific data submitted for the plant incorporated protectants and many of the currently registered microbial and biochemical pesticides. Dr. Kough has presented EPA's position at numerous Scientific Advisory Panels on topics like product characterization, protein toxicity assessment and food allergenicity. He has also helped write sections of EPA's plant-incorporated protectants rule as well as policy on pheromone-based pesticides. Dr. Kough recently received EPA's Seifter Award for his role in the human health risk assessment of the products of biotechnology. Dr. Kough has published numerous papers on the regulation of biopesticides as well as his research interests of biological control and immunology. Prior to joining EPA, John was a research project director at IGEN, a biotechnology company specializing in developing monoclonal antibodies for several plant diseases. John received a B.A. degree in biology from Reed College in Portland, OR and a Ph.D. degree in plant pathology from Oregon State University. Dr. Kough received an NSF post-doctoral fellowship in Dijon, France where he researched the ecology and biocontrol of soil borne fungi. John was born in Uniontown, PA and raised in the Allegheny Mountains of southwestern Pennsylvania.

Mary Ditto: Dr. Mary Ditto is a Consumer safety Officer for the United States Food and Drug Administration (FDA). She received her Ph.D. in Molecular Genetics and Cell Biology from the University of Chicago and did post-doctoral research work at the National Institutes of Health. She currently serves as a Consumer Safety Officer in the Division of Biotechnology and GRAS Notice Review, which is part of the Center for Food Safety, and Applied Nutrition in FDA. She has worked on biotechnology issues for several years.

Janet Whitley: Dr. Janet Whitley has been a reviewing scientist with the Office of Orphan Products Development at the Food and Drug Administration (FDA) since 2000. At FDA she administers the provisions of the Orphan Drug Act which facilitates development for medical products for the treatment of rare diseases. Dr. Whitley serves as a project manager for international orphan drug policy development. Outside of FDA, Dr. Whitley is an adjunct faculty member at the University of Maryland, University College where she teaches Biotechnology and the Regulatory Environment.

Dennis Gonsalves: Dr. Dennis Gonsalves is the Director, USDA ARS – Pacific Basin Agricultural Center in Hilo, Hawaii. He holds a Ph.D. in Plant pathology from the University of California, Davis. From 1972-1977, he worked on viruses that affect citrus at the University of Florida, advancing from assistant to associate professor. He then joined Cornell University at the New York State Agricultural Experiment Station in Geneva, New York and worked there from 1977 to May 2002. While at Cornell, he worked on viral diseases of fruit and vegetable crops, with an emphasis on developing genetically engineered plants to control viral diseases. He became a full professor in 1986 and was appointed to one of the endowed Liberty Hyde Bailey Professor positions in 1995. While at Cornell, Dennis maintained close research ties with the University of Hawaii and led a team to develop and commercialize a transgenic papaya that helped to save the papaya industry from devastation by the papaya ringspot virus. The initial team consisted of Drs. Richard Manshardt of University of Hawaii, Maureen Fitch of ARS, and Jerry Slightom of Pharmacia-Upjohn with Steve Ferreira of the University of Hawaii playing a major subsequent role. For the papaya

work, the initial team was awarded the Alexander Von Humbolt Award in 2002. Dennis recently received the 2003 American Society of Plant Biologist Leadership in Science and Public Service Award.

Ralph Scorza: Dr. Ralph Scorza is a Horticultural Researcher, USDA – ARS Appalachian Fruit Research Station. He received his undergraduate degree in agronomy at the University of Florida. After a tour in the Peace Corps in the Amazon region of Brazil, working with tropical fruit production, he returned to the University of Florida and received his Ph.D. from Purdue University in Plant Genetics and Breeding under the guidance of Dr. Jules Janick. Following an assignment in Bolivia, where he worked for the University of Florida, Dr. Scorza was hired by the USDA as a stone fruit breeder at the USDA – ARS Appalachian Research Station since 1980. He has released Sentry and Bounty peaches, now widely grown in the northeastern U.S., Earliscarlet nectarine, and, most recently, Bluebyrd plum. Dr. Scorza has developed new columnar growth habit peaches for high-density production systems and these are currently under test in a number of states.

In the mid 1980's Dr. Scorza initiated a tree fruit biotechnology program at the Appalachian Fruit Research Station to supplement conventional breeding for variety development. The program has developed gene transfer systems for plum, grape, and pear. Aware of the potential consequences of an introduction of plumpox virus into the U.S., Dr. Scorza initiated a program to develop plum pox virus resistant transgenic plums.

Alan McHughen: Dr. Alan McHughen is *a* Plant Biotechnologist at the University of California, Riverside. Dr. McHughen's research focuses on using biotechnology, especially the development of molecular genetic technology to develop improved crops contributing to more environmentally sustainable cropping systems. He is also interested in analyzing products of biotechnology for their effects on the environment and on health.

Alan McHughen is a public sector educator, scientist and consumer advocate. After earning his doctorate at Oxford University and working at Yale University, Dr. McHughen spent twenty years as Professor and Senior Research Scientist at the University of Saskatchewan before joining the University of California, Riverside. A molecular geneticist with an interest in crop improvement, he has helped develop Canada's regulations covering the environmental release of plants with novel traits and US regulations governing transgenic plants. He served as recent OECD (Organization for Economic Cooperation and Development) panels investigating the health effects of genetically modified foods. Having developed internationally approved commercial crop varieties using both conventional breeding and genetic engineering techniques, he has first hand experience with issues from both sides of the regulatory process, covering both recombinant DNA and conventional breeding technologies. He also served on the Canadian national expert committee on variety registration (including several years on the executive panel as Secretary of Oilseeds Subcommittee). As an educator and consumer advocate, he helps non-scientists understand the environmental and health impacts of both modern and traditional methods of food production. His award winning book, 'Pandora's Picnic Basket; The Potential and Hazards of Genetically Modified Foods', uses understandable, consumer-friendly language to explode the myths and explore the genuine risks of genetic modification (GM) technology.

David Clark: Professor of Floriculture Biotechnology, University of Florida The research in Dr. Clark's laboratory is directed toward genetic engineering of floriculture crops for improved horticultural performance during production and post harvest handling. Dr. Clark's specific interests are in the areas of post harvest physiology, and molecular biology of ethylene biosynthesis and sensitivity in flowers. The main goal of his work is to utilize information gained from molecular and physiological experiments to help solve real-life problems in greenhouse-grown floriculture crops. He hopes to determine the commercial viability of genetically engineered floriculture crops by assessing the attributes and limitations of genetically engineered floriculture crops in commercial scale greenhouse experiments**.**

Keith Redenbaugh: Dr. Keith Redenbaugh is the Associate Director of Regulatory Affairs, Seminis Vegetable Seeds. Dr. Redenbaugh has been involved with agricultural biotechnology since the mid 1970's. At Calgene, he worked with the FDA and USDA to establish appropriate instruments for safety assessment and oversight of transgenic crops and foods. He obtained regulatory approvals for the first transgenic whole food, the FLAVR SAVR tomato. His efforts also led to FDA issuing a food additive regulation for the kanamycin-resistant marker gene protein, NPTII, a significant decision by the FDA. He also obtained for the FLAVR-SAVR tomato what is still the only full commercial approval of a transgenic crop in Mexico. Dr. Redenbaugh spent 1 1/2 years at Iowa State University in the role of Biotechnology Industry Liaison, which involved broad biotechnology interactions with industry and the public, ranging from issues on fermentation, animal health, transgenic animals, as well as plant biotechnology. In this role, Dr. Redenbaugh spent time talking to farmers, students (both high school and college), and community service organizations.

Currently, Dr. Redenbaugh is Associate Director for Regulatory Affairs, Licensing and contracts at Seminis Vegetable Seeds. His responsibilities include worldwide regulatory affairs, commercialization of biotech plants, biotechnology stewardship, technology assessment, and negotiating licensing and contracts for the R&D department.

Terry Stone: Terry Stone is the Director – Biotechnology and Regulatory Affairs at Scott's. Terry Stone obtained his Bachelor's degree from Southern Illinois University in invertebrate zoology and holds a Master of Science degree in Entomology from Mississippi State University and a Masters degree in International Business from St. Louis University. For 19 years he worked at Monsanto to develop and commercialize plants through biotechnology with resistance to insects and tolerance to Roundup herbicide. For the past 12 years he has worked in biotechnology regulatory affairs and helped to gain approval for a number of products including NewLeaf potatoes, Bollgard cotton and YieldGard corn. In 2001, he began leading an effort to gain the regulatory acceptance of specialty crops, including turfgrasses, developed through biotechnology. He left Monsanto in April 2003 to join The Scotts Company in Marysville, Ohio to focus on biotech-derived turf and ornamentals and currently serves as the Director of Biotechnology Regulatory Affairs.

Maud Hinchee: Dr. Hinchee has been the Chief Technology Officer at ArborGen since 2000, and before that she had spent many years at Monsanto, where she conducted research in the field of biotechnology. Some of her professional activities include being Managing Editor of The Plant Biotechnology Journal, and Managing Editor of Plant Cell, Tissue and Organ Culture. Dr Hinchee was on the Board of Reviewing Editors for In Vitro Cellular and Developmental Biology as well. She has authored five patents and over twenty scientific publications including a plant biology textbook**.**

Les Pearson: Dr. Pearson has been the Director of Regulatory Affairs and Regulatory Science, ArborGen, LLC, since 2002. He is responsible for regulatory oversight for ArborGen field trials. ArborGen is a world leader in transgenic forest tree research. ArborGen conducted the first field trials of *Eucalyptus* in the US and is currently the only entity field-testing transgenic *Eucalyptus* and pine in the US and sweetgum worldwide. Prior to joining ArborGen Dr. Pearson was the Biotechnology Section Leader for Westvaco Forest Research (1998-2000), where he had oversight of world's first field trials of transgenic pine. From 1989-1997 he was Senior Scientist DNA Markers / Project Leader Molecular Genetics, Westvaco Forest Research. Les received a Ph.D. from the John Innes Institute, Norwich, England in 1983, where he demonstrated the relationship between DNA methylation and gene expression in plants. He served as a Post-doctotal research fellow at the University of Georgia from 1984-1989, where he studied gene expression of the actin multi-gene family in soybeans.

Robert Holm: Dr. Bob Holm was raised on a small farm in Indiana and received his B.S, M.S. and Ph. D. degrees (Biochemistry and Plant Pathology) from Purdue University. Prior to joining IR-4 as Executive Director in 1998, Dr. Holm spent 30 years in the crop protection industry working for Diamond Shamrock Corporation as a Senior Research Scientist; Mobil Crop Chemical as Research Manager; Rhone-Poulenc as Director of Agrochemical Sciences and Field Research and Product Development; and Valent U.S.A. Corporation, a Sumitomo Chemical Company subsidiary, as Technology Vice-President. He has had extensive experience with the development of crop protection tools on a wide variety of major row crops as well as numerous specialty crops like fruits and vegetables. Dr. Holm is a member of a number of professional societies and served as Chairman of the Plant Growth Society of America in 1978/1979. Five patents have been issued in his name. He has over 40 technical publications and book chapters in referred journals and has given over 200 presentations at various professional and technical society meetings.

Sarah Linde-Feucht: Dr. Linde-Feucht is a Medical Officer at Office of Orphan Products Development at the US Food and Drug Admiistration. Sarah R. Linde-Feucht is a medical officer assigned to the Food and Drug Administration Office of Orphan Products Development. There, she directs the Humanitarian Use Device program and is the administrator for the Grants Program. Prior to her assignment with FDA, Dr. Linde-Feucht was assigned to the National Health Service Corps and served as the Director of the Shenandoah Valley Family Health Center, a community health center in Inwood, WV. Prior to that, she worked as a staff medical officer at the Shenandoah Valley Medical Center, another community health center, in Martinsburg, WV.

Dr Linde-Feucht is board certified in Family Practice and is a graduate of the Uniformed Service University of the Health Sciences Medical School in Bethesda, MD. She was commissioned to the Public Health Service in 1988 and has been very active in many Public Health Service activities, such as the Physicians Professional Advisory Committee, the Disaster Medical Assistance Team, and the Commissioned Appointment Readiness Force. She has also served on the Medical Professional Category Appointment Board and the Medical Review Board. She is a member of the COA and the recipient of the Clinical Physician of the Year Award presented at the 1998 COA meeting.

Steven Strauss: Dr. Steven Strauss is a Professor of Forest Sciences at Oregon State University. Dr. Strauss's research is on the application of molecular genetic methods to the genetic improvement and analysis of forest trees. He has a major research effort in association with several paper and energy industries on genetic engineering of poplar trees, population genetics of conifers using organelle and nuclear genome markers, and constructing genome maps of Douglas-fir to identify genes that control growth and adaptation.

Current tree projects include development of more efficient means for gene transfer; testing of genes for resistance to the herbicide Roundup® in transgenic poplars; testing genes for insect resistance and means for their safe deployment; and genetic engineering of trees for complete reproductive sterility. The latter project is motivated by desire for genetic containment of inserted genes from wild populations. Included in the sterility work are sub-projects on early flower induction, isolation and study of floral homeotic gene expression from poplars, and testing of transgenic trees for sterility. Six floral homeotic genes have been cloned and are now being intensively characterized; they are evolutionary homologs to the floral homeotic genes *agamous, leafy, apetala1* and *apetala3* from Arabidopsis.

Jeff Wolt: Dr. Jeff Wolt is Professor of Agronomy at Iowa State university. Dr. Wolt's areas of expertise are as follows: biotechnology safety analysis applied to risk management and science policy decision-making, environmental and ecotoxicological risk assessment, soil and environmental chemistry applied to exposure assessment, efficacy, environmental monitoring, environmental toxicology, and environmental fate of xenobiotics.

Dr. Wolt conducts research in biotechnology risk assessment with emphasis on uncertainty analysis using probability and possibility theory, ecological consequences of pollen and gene flow, and risk management and communication. Earlier research centered on method development and application of soil solution compositional analysis to problems of environmental monitoring and ecological exposure assessment. Dr. Wolt directed a discovery support effort to evaluate efficacy/environmental sorption/degradation processes, elucidation of solute flow paths through the soil profile, methods of enhancement of retardation/degradation within the soil profile, modeling evaluation of environmental fate and ecotoxicity in ground and surface water.

Neal Gutterson: Dr. Neal Gutterson currently serves as the Chief Operating Officer and Senior Vice President, Research and Development, for Mendel Biotechnology, Inc. Mendel is a leading plant genomics company, dedicated to creating new plant and chemical products based on knowledge of plant pathways. Prior to joining Mendel, Dr. Gutterson spent 18 years at DNA Plant Technology, a leading plant biotechnology company, beginning with 5 years at Advanced Genetic Sciences, later acquired by DNAP. Dr. Gutterson's roles included: project leader for the development of transgenic biological control products based on fluorescent pseudomonads; project leader for an ornamentals program focused on modification of flower color and shelf life; Director of Research in new crops and technologies, focused on specialty crops, and transgenic methodologies; and later Vice President of Research.

Dr. Gutterson's research areas have included: the regulation of plant gene expression; development of plant transformation vectors and transformation methods; methods of gene silencing, with a focus on sense suppression; plant disease resistance; plant pathways and transcription factors. He has published more than two dozen research articles; he is a named inventor on 10 U.S. patents, and more than a dozen pending U.S. patent applications. He holds a Ph.D. in Biochemistry from the University of California, Berkeley, and a B.S. in Chemistry from Yale University.

Alan McHughen: Alan McHughen is a public sector educator, scientist and consumer advocate. After earning his doctorate at Oxford University and lecturing at Yale University, Dr McHughen worked at the University of Saskatchewan before joining the University of California, Riverside. A molecular geneticist with an interest in applying biotechnology for sustainable agriculture and safe food production, he served on recent National Academy of Science, Institute of Medicine and OECD panels investigating the environmental and health effects of genetically novel plants and foods. Having developed internationally approved commercial crop varieties using both conventional breeding and genetic engineering techniques, he has first hand experience with issues from both sides of the regulatory process, covering both recombinant DNA and conventional breeding technologies. McHughen also served for six years as President of the International Society for Biosafety Research.

Appendix B: Workshop Participants

First name	Last name	Title	Affiliation	Work Location
Herbert	Aldwinkle	Professor - Plant Pathology	Cornell University	NY
Victor	Amoah	Research Consultant	Citrus Research Board	CA
George	Acquaah	Researcher	Langston University	OK
Ted	Batkin	President	Citrus Research Board	CA
Alan	Bennett	Professor	PIPRA at University of Calfornia Davis	CA
Kent	Bradford	Professor	University of California - Davis	CA
Samuel	Besong	Coordinator - Center for Biotechnology	Alcorn State University	MS
Dan	Cantliffe	Chair - Department of Horticulture	University of Florida	FL
Janet	Carpenter	Biotechnolgy Advisor	USAID	DC
Elicia	Chaverest	Research Associate - Department of Agribusiness	Alabama A & M University	AL
Duncan	Chembezi	Co-Director - Small Farms Research Center	Alabama A & M University	AL
David	Clark	Professor	University of Florida	FL
Joel	Cohen	Director - Biosafety Systems	IFPRI	DC
Greg	Conko	Director - Food Safety Policy	Competitive Enterprise Institute	DC
Jim	Cook	Professor	Washington State University	WA
John	Cordts	Biotechnologist	USDA-APHIS	MD
Katrina	Cornish	Senior Financial Executive	Yulex Corporation	CA
Carole	Cramer	Director - Arkansas Biotechnology Institute	Arkansas State University	AR
Deborah	Delmer	Associate Director of Food Safety	Rockafeller Foundation	NY
Mary	Ditto	Consumer Safety Officer	FDA	DC
Michael	Dobres	President and CEO	NovaFlora Inc.	PA
Hortense	Dodo	Researcher	Alabama A & M University	AL
Steve	Duke	Supervisor	USDA-ARS	MS
Mary	Duryea	Assistant Dean for Research	FAES, IFAS/University of Florida	FL
Jose	Falck-Zepeda	Research Fellow	IFPRI	DC
Mike	Fernandez	Director of Science	Pew Initiative on Food and Biotechnology	DC
Sharie	Fitzpatrick	Director of Regulatory Affairs	Forage Genetics International	WI
Vicki	Forster	Principal	Forster & Associates Consulting, LLC	DE
Bob	Frederick	Senior Scientist	EPA	DC
Tom	Fretz	Executive Director	NERA	MD
Sarah	Linde-Feucht	Medical Officer	FDA	MD
Dale	Gallenberg	Director - Plant Sciences	South Dakota State University	SD
Jeanette	Glew	Enivronmental Scientist	FDA	DC
Dennis	Gonsalves	Center Director	Pacific Basin Agricultural Center	HI
Elizabeth	Grabau	Professor	Fralin Biotechnology Center and Department of Plant Pathology	VA
Neal	Gutterson	Chief Operating Officer	Mendel Biotechnologies	CA

Deb	Hamernik	Program Leader - Plant and Animal Systems	USDA-CSREES	DC
Freddi	Hammerschlag	Supervisor	USDA-ARS	MD
John	Hammond	Research Leader	USDA-ARS	MD
Levis	Handley	Biotechnologist	USDA-APHIS	MD
Michael	Harrington	Executive Director	WAAESD	CO
Zane	Helsel	Extension Specialist	Rutgers University	NJ
Maud	Hinchee	Chief Technology Officer	Arborgen	SC
Neil	Hoffman	Regulatory Agency	APHIS	MD
Bob	Holm	National Dir of IR-4 Project	IR-4 at Rutgers University	NJ
Elizabeth	Hood	Associate Vice Chancellor - Research and Technology Transfer	Arkansas State University	AR
Greg	Jaffe	Director of Biotechnology	Center for Science in the Public Interest	DC
Margaret	Jahn	Professor	Cornell University	NY
Alberto	Jerardo	Economist	ERS	DC
Eluned	Jones	Director	Texas A&M	TX
Eileen	Kabelka	Associate Professor	Univ of Florida	FL
Frederick	Keter	Student	University of Maryland Eastern Shore	MD
Lawrence	Kent	Director - International Programs	Danforth Center	MO
Harry	Klee	Professor	University of Florida	FL
John	Kough	Senior Scientist	EPA	DC
Gary	Lemme	Associate Director	Michigan Agricultural Experiment Station	MI
Richard	Levine	Consultant	Better Earth Communications, Inc.	MD
Josette	Lewis	Chief Biotechnology Officer	USAID	DC
Nicholas	Linacre	Post Doctoral Fellow	IFPRI	DC
Jiang	Lu	Researcher	Florida A & M University	FL
Bob	Martin	Researcher	USDA-ARS	OR
Marshall	Martin	Associate Director - Agricultural Research Programs	Purdue University	IN
Adrianne	Massey	Principal	Massey and Associates	NC
Kanyand	Matand	Researcher - Forage grass	Langston University	OK
John	Matheson	Senior Regulatory Review Scientist	FDA/CVM	MD
Sally	McCammon	Science Advisor	USDA-APHIS	MD
Mark	McCaslin	President	Forage Genetics International	MO
Alan	McHughen	Biotechnologist	University of California - Riverside	CA
Sreenivasa Rao	Mentreddy	Associate Professor - Crop Sciences	Alabama A & M University	AL
Hodeba	Mignouna	Associate Professor	Virginia State University	VA
Craig	Nessler	Head of Dept of Plant Pathology	Virgnia Tech	VA
Jay	Norelli	Plant Pathologist	USDA-ARS	WV
Okeleke	Nzeogwu	Associate Professor - Department of Agriculture	University of Maryland - Eastern Shore	MD
Paul	Olson	Research Scientist	Pioneer	IA
Eldon	Ortman	IPA/NPL	CSREES-USDA	DC
Peggy	Ozias-Akins	Professor of Horticulture	University of Georgia	GA
Bhavani	Pathak	Biotechnology Advisor	USAID	DC

Les	Pearson	Director - Regulatory Affairs	Arborgen	SC
Jane	Polston	Professor - Plant Pathology	University of Florida	FL
Steven	Pueppke	Professor - Plant Genetics	University of Illinois	Ill
Hector	Quemada	BBI Program Manager - Biosafety Systems	Western Michigan University	MI
Umesh	Reddy	Researcher	Alcorn State Univ	MS
Keith	Redenbaugh	Associate Director - Regulatory Affairs	Seminis Vegetable Seeds	CA
Carlos	Reyes	US Markets Specialty Crops	Monsanto	CA
Sandra	Ristow	Associate Director	Washington State University	WA
Ray	Rodriguez	Professor	University of California - Davis	CA
Rick	Roush	Professor-Entomology	University of California - Davis	CA
Larisa	Rudenko	Senior Advisor on Biotechnology	FDA	MD
Eric	Sachs	Director - Scientific Affairs	Monsanto	MO
Michael	Schechtman	Biotech Coordinator	USDA-ARS	DC
Ralph	Scorza	Researcher	USDA-ARS	WV
Roger	Sedgo	Senior Fellow	RFF	DC
Ken	Sink	Director - Plant Transformation Center	Michigan State University	MI
Ann	Smigocki	Research Geneticist	USDA-ARS	MD
John	Stiles	Chief Scientific Officer	Integrated Coffee Technologies	HI
Mark	Stowers	President and CEO	MBI International	MI
Terry	Stone	Director of Biotechnology and Regulatory Affairs	Scott's	OH
Steven	Strauss	Professor - Department of Forest Sciences	Oregon State University	OR
Hollee	Stubblebine	Director - Industry Communications	National Potato Council	DC
Christian	Studlein	Chairman	Integrated Coffee Technologies	HI
Kathy	Swords	Manager - Business Development	Simplot Plant Sciences	ID
Scott	Thenell	Biotechnology Regulatory Affairs	Consultant	CA
Cheryl	Toner	Director - Health Communications	International Food Information Council	DC
David	Tricoli	SRA Supervisor	University of California - Davis	CA
George	Ude	Plant Breeder	Bowie State University	MD
Michael	Wach	Biotechnlogist	USDA-APHIS	MD
David	Williams	Senior Vice President - Operations	Cholorgen	MO
Janet	Whitley	Researcher	Orphan Drugs Program - FDA	DC
Jeffrey	Wolt	Professor - Soil Chemistry	Iowa State University/BIGMAP Program	IA
Ning	Wu	Professor	Langston University	OK
Paul	Zankowski	Commissioner	USA-PVP	MD
David	Zilberman	Professor - Agricultural Economics	University of California - Berkeley	CA
Steering Committee				
June	Blalock	Coordinator -Technology Licensing Program	USDA-ARS	MD

Marvin	Burns	Dean - School of Agriculture and Applied Sciences	Langston University	OK
William	Goldner*	National Program Leader - SBIR	USDA-CSREES	DC
Daniel	Jones	National Program Leader - Biotechnology	USDA-CSREES	DC
Ed	Kaleikau	National Program Leader - Competive Programs	USDA-CSREES	DC
Jill	Long Thompson	CEO and Senior Fellow	NCFAP	DC
John	Radin	Crop Production - Product Value and Safety	USDA-ARS	MD
Sujatha	Sankula	Director of Biotechnology Research	NCFAP	DC
Ann Marie	Thro*	National Program Leader - Plant and Animal Systems and Steering Committee Chair	USDA-CSREES	DC

*Steering Committee Co-Chair

Appendix C: Workshop Agenda

Monday, 8 November 2004

8:00-8:30 Continental breakfast and registration

8:30-8:35 Call to order, Adrianne Massey, Principal, A. Massey and Associates

8:35-8:40 Welcome message, Jill Long Thompson, CEO and Senior Fellow, NCFAP

8:40-8:45 Welcome message, Colien Hefferen, Administrator, USDA-CSREES

8:45-8:50 Welcome message, Marvin Burns, Dean, School of Agriculture and Applied Sciences, Langston University

8:50-8:55 Welcome message, Edward Knippling, Associate Administrator, ARS

8:55-9:00 Workshop purpose/challenge at hand, Ann Marie Thro, CSREES

9:00-9:15 Overview of a Workshop (June 2004) co-organized by Pew Initiative on Food and Biotechnology and USDA-APHIS on "Impacts of biotechnology regulation on small business and university research – possible barriers and solutions", Michael Fernandez, Pew Initiative on Food and Biotechnology

9:15-10:15 Overview session - Economic Research Service, USDA, and regulatory agencies
Moderator: Dan Jones, CSREES

- Alberto Jerardo, Economic Research Service
- Sally McCammon, Animal and Plant Health Inspection Service
- John Kough, Environmental Protection Agency
- Mary Ditto, Food and Drug Administration

10:15-10:35 Panel and audience discussions (A. Massey, Facilitator)

10:35-11:00 Break

11:00-12:00 Regulatory challenges - Experiences from the perspective of public researchers
Moderator: John Radin, ARS

- Dennis Gonsalves, ARS (virus-resistant papaya)
- Ralph Scorza, ARS (virus-resistant stonefruit)
- Alan McHughen, University of California-Riverside (herbicide-tolerant flax)
- David Clark, University of Florida (Petunias with delayed flower senescence)

12:00-12:20 Panel and audience discussions (A. Massey, Facilitator)

12:20-1:20 Lunch

1:20-2:20 Regulatory challenges **-** Viewpoints from the perspective of private business enterprises
Moderator: Bill Goldner, CSREES

- Keith Redenbaugh, Seminis
- Neal Gutterson, Mendel Biotechnology
- Terry Stone, Scotts
- Les Pearson, ArborGen

2:20-2:45 Panel and audience discussions (A. Massey, Facilitator)

2:45-3:15 Break

3:15-4:00 Approaches to regulatory realities – a look into existing models
Moderator: June Blalock, ARS

- Bob Holm, IR-4 Program
- Sarah Linde-Feucht, Orphan Drug Program, FDA

4:00-4:45 Approaches to regulatory realities – exploration of possible new models

- Steven Strauss, Oregon State University
- Jeff Wolt, Iowa State University

4:45-5:15 Panel and audience discussions (A. Massey, Facilitator)

5:15 Adjourn

Tuesday, 9 November 2004

8:00-8:25 Reconvene and continental breakfast

8:25-8:30 Review of goals for the day (A. Massey, Facilitator)

8:30:10:30 Brainstorming for solutions to surmount challenges and identify alternative scenarios

- Breakout Session Question 1: Critical crops and traits that need to move through regulatory process
- Breakout Session Question 2: Areas of research that could enhance and accelerate the deregulation of small market crops
- Breakout Session Question 3: The appropriateness of existing models to overcome the barriers and identify new models or propose changes to existing models
- Breakout Session Question 4: Identification of next steps including how we can address the issues raised

10:30-10:45 Break

10.45:12:15 Report from Breakout Groups and Discussion - (A. Massey, Facilitator)

12:15-1:15 Lunch

Working lunch for breakout group leaders and steering committee to prepare first draft of recommendations based on breakout group reports

1:30-2:15 Discussion and development of second draft of workshop recommendations (A. Thro, CSREES)

2:15-2:40 Finalization of workshop recommendations (A. Massey, Facilitator)

2:40-2:45 Closing remarks: Ann Marie Thro, CSREES

Adjourn