Module III
Gene-to-Product Development

Panel Discussion and Q&A

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William Goldner: I'll take a few minutes to introduce you to the Specialty Crops Regulatory Initiative—a USDA-sponsored program now getting underway. I believe it's germane to the topics that we've been discussing. It's a program that came to us based on the output of a biotechnology workshop held in November of 2004 that I chaired with Ann Marie Thro, sponsored by the Agricultural Research Service, Cooperative State Research Education and Extension Service and the Animal and Plant Health Inspection Service. The workshop was in response to the frustration that small business and public developers of specialty biotechnology crops have felt in terms of being unable to get their products—the crops they have developed—to market. And as we've seen today, including Beth Hood's representation of what it takes to get a product to market, there are many hoops to go through as a crop developer. And university researchers, ARS researchers and small-business developers of biotechnology crops generally are not prepared to address these issues. It takes a good deal of expertise, involving navigating a regulatory process that is always in some state of evolution with interaction with as many as three federal agencies, the FDA, EPA and APHIS itself. Only a few of the specialty crops have been deregulated and that's really the issue that came up in the workshop—the need for an organization to assist public-sector and small-scale private-sector developers through the regulatory approval process. And there is precedence for this; the orphan-drug program in FDA assists pharmaceutical companies in bringing through the regulatory process drugs that serve only a small population of patients because of disease rarity. Also the USDA's IR-4 program addresses the needs for small-acreage pesticide use and assists companies to develop datasets that meet the regulatory process to gain approval for use on minor crops.

Roger Beachy and Mike Rodemeyer mentioned issues of management and stewardship that we as scientists are ill-equipped to deal with on a day-to-day basis. So, the concept is to develop the Specialty Crops Regulatory Initiative to identify and prioritize need and public benefit, helping to facilitate the generation of required regulatory safety data for fruits and nuts, vegetables, ornamentals, nursery crops, even forest trees (anything but the four major row crops). This is analogous to what happens in the IR-4 program for specialty pesticides. The idea is to facilitate the process and has nothing to do with the ultimate commercialization or marketing of biotechnology crops or the products from those crops.

The structure mimics that of the IR 4 program in that three committees are proposed: a stakeholder/liaison group, a project-management group and ultimately a headquarters staff. A critical aspect is involvement of and partnership with several different communities: consumer groups, grower groups, distributors, university researchers and technology groups as well as government researchers and administration. The near-term challenges are clear. We must demonstrate an early ability to enable regulatory compliance for a new biotechnology-derived crop. Based on discussions so far, perhaps a non-food crop would be the most suitable target. In fact, a crop from outside the United States—one that would benefit a developing country—could be the target.

A long-term challenge is to make available a broader range of biotechnology crop options for public benefit, meeting economic and environmental needs. We'd welcome input from those involved in crop-development and also in the other aspects such as marketing and commodity groups. We can send you information on the initiative. There is a national planning committee and Beth Hood and I are members; Alan McHughen at the University of California, Riverside, is the national chairman. Also on the committee are representatives of the Agricultural Research Service, APHIS, CSREES, land-grant universities, the private sector and also of some commodity groups. A follow-up workshop will convene in November of 2005 specifically to address the needs and requirements and suggestions of the stakeholders to help us craft and develop this important organization.

Alex Day: I'm with the Kentucky Life Sciences Organization. I also founded a company called Sheltowee LLC. We do life-science business consulting and business development. I want to talk about what I see as a couple of obstacles that we face in bringing products to the market. The biggest obstacle is regulatory. Particularly for the pharmaceutical and health uses of some of these proteins, we haven't been able to convince the regulators to show us the path. When I first became an entrepreneur I was told, "Remember, the pioneer is known as the guy with all the arrows in his back." We can't even seem to find a pioneer who can get all the way through the process and take the arrows so that we know how to get the products through. So, we are dealing with a public-perception problem but also a problem with the regulatory agencies reacting to public perception. Another common problem is early-stage funding. I know that in our state it's very difficult to bring in seed-stage funding. The definition of seed-stage funding has changed dramatically over the past few years. There are very few venture-capital or other sources willing to make seed-stage investments.

Another issue for early-stage products is meshing business with science. I'm more of a business person. I know enough of the science to be dangerous and to understand some of what's discussed in forums like this. The science must be translated into terms that business people are going to understand, providing compelling reasons to put the money in to develop the products. That cross-talk—meshing business and science—is critical to taking products through the development process and bringing them to market. The Kentucky Life Science Organization—a non-profit trade organization—is trying to educate people all the way from the grass-roots level up to politicians as to why these things are important and what we can do to facilitate, to clear a path so that these products can be brought to market.

Roger Conway: I want to discuss the need for a general field theory for commercialization. There has been a lot of frustration in the bioproducts and bioenergy areas. Some people have felt that we've done a lot of research, but haven't accomplished as much as we'd like to. I'd argue that there might be under-investment and other links in a causal chain. You might want to think of it as a pipeline of different links that need to be looked at for commercialization. And, of course, research is important—the plant genomics, the conversion work is very important. We want to lower the cost of production, we want to increase yields—that's an important component—but other things are important too: for example, having life-cycle analyses from cradle to grave to show environmentalists that these products are environmentally beneficial. This is something that is featured in our federal biobased-products-preferred procurement program that my office is responsible for. In addition, having ASTM/ISO-compliant standards is important for demonstrating to potential buyers that your product really works, and in some cases in the bioproduct industry that hasn't been done and needs to be done. We've dealt with the Defense Logistics Agency who are fastidious about the products they buy; when they put a lubricant in a army tank that's going to Iraq they want to be sure it works. These are potentially huge markets, but the need for testing is extremely important. So that's another link.

Another link is in terms of regulatory initiatives. For example, the main reason that the ethanol industry has doubled recently is because of the reformulated gasoline program, which requires oxygenates. In California, MTBE has been replaced with ethanol—as a regulatory initiative—which has virtually doubled the use of ethanol. Other things can be done. For example, Lou Honary at the University of Northern Iowa has developed transformer fluids from soybean oil. There is a problem with fossil-fuel-based transformer fluids containing PCBs. Perhaps EPA could differentiate between bioproducts and fossil-fuel products based on toxicity, biodegradability and flashpoint. We will continue dialog with EPA on these issues.

Another link is product differentiation and commercialization, and the Federal Biobased Products Preferred Procurement Program that we are running is an opportunity for product scale-up because it offers a guaranteed market. It's an opportunity for the private sector to see what's happening in the public sector as we use these products and could greatly expand markets.

Another link is public-sector initiatives such as investment tax credits, which are highly effective, and the USDA CCC Bioenergy Program for example. The latter is responsible for creating the biodiesel industry as it is today. Before the Program, biodiesel consumption was approximately 2 million gallons now it's up to around 60 million gallons. The USDA can take pride in helping to advance that industry.

Financing issues are also important. Especially for rural areas, obtaining capital continues to be a problem. Having some sort of public-private cooperation may be useful. Having access to specialized insurance may help reduce the risk. Once again, tax-credit issues may help.

Finally, education and outreach: science-based outreach to the public sector is necessary, one that explains environmental issues and also explains the performance characteristics of these products.

So, in the past we may have under-invested in some of these links and I'd argue that we need to view this thing in a more holistic fashion. Research is absolutely important, but there are other features that can help get these products to the market.

Allan Bennett (University of California, Davis, CA): For Beth. I was impressed with the seventy-five licenses for your product and I'm wondering if you have a sense of how many of them were actually required for FTO and the final product. Do you have any sense of the financial burden of those licenses on the TrypZean™?

Elizabeth Hood: A lot of the licenses were for our transformation system, promoters, leader sequences, trailer sequences and the selectable marker genes. Probably, some of them were package deals that we were able to bring with us from Pioneer—pass-through licenses, *etc*. I would say that the majority had an impact on the product. The financial burden? I couldn't tell you because I think each set of them had a different percent royalty based on sales in some cases and based on a flat fee in others. Therefore, the more products you develop the less the burden is on any one particular product. It's important to have those licenses so that you can legally market the product. But you don't pursue seventy-five licenses with the objective of only one product. You assume you're going to have a pipeline of products.

Goldner: Do you anticipate any phenotypic effect from lowering the lignin content in the softwood or hardwood trees?

Hinchee: The process of product development is to put the trees in the field and then assess them for all the usual performance characteristics in terms of a breeding program and a clonal development program. Are they stress-tolerant? Are they disease-resistant? Do they perform like the non-transgenic trees with the exception of the reduced lignin trait? Our anticipation is that if we launch a softwood or a hardwood product with reduced lignin that it would be within a range that allows the pulping industry to benefit from that advantage, but doesn't affect any of the other phenotypic characteristics and the health of the plantation can be maintained.

Ralph Hardy (NABC, Ithaca, NY): Will your reduced lignin trees now make it possible for new pulp and paper mills to be built in the United States? It's my understanding that there hasn't been a pulp and paper mill built in the United States for a long time because of the extensive costs of pollution control plus processing. Are you reducing lignin, capital and/or operating costs enough? And can you give us some range of what that might be? Is it a compelling number or a marginal number?

Hinchee: It's analyzed on a mill basis and is premised on the fact that no more mills will be built in the United States. We are talking in terms of saving the US forestry and pulp and paper industries. They are looking for anything to improve efficiency because the profit margin is small and they are facing abundant supplies of wood from Siberia and other places where they are indiscriminately harvesting very old trees. To maintain the industry in the United States they must improve efficiency in a variety of ways. Genetic improvement is actually a no-cost opportunity to improve efficiency without major investment at the mill, apart from normal adjustments of boilers for lignin extraction for the variety feedstocks that come in already. It's using genetics to enhance the survivability of an industry, in my opinion.

Allan Eaglesham (NABC, Ithaca, NY): Following on from Dr. Goldner's question: is it possible to reduce lignin level to zero? And if not, is there potential to reduce it farther than what you've achieved already?

Chiang: The maximum is a 50% lignin reduction. We've produced 200 or 300 transgenic trees with low lignin and never got more than a 50% reduction. I believe that is related to total carbon-sink control regulating the three major cell-wall components: lignin, cellulose and hemicellulose. Low-lignin content has also been found in apple in nature. It was considered to be disease-related, but it's not. It's just a low lignin content, again about 50% lower than normal apple trees.

Jensen: Anybody have a question for our panelists?

Svetlana Oard (Louisiana State University, Baton Rouge, LA): What change would the panelists make in the regulations to expedite the gene-to-production process?

Conway: As a USDA representative, it's really not up to me to give an opinion about the regulations of our sister agencies and of other federal agencies, but I think it's clear that there is potential for some regulatory evolution, using a science-based rational approach. That seems to be the consensus from everybody I've talked to here.

Day: Being the non-government guy, I'd be happy to provide all kinds of advice to FDA. We believe that the best opportunity for plant-based pharmaceuticals is probably going to be generic biologics. Provide us the guidelines for meeting bioequivalency. Those products are being produced in plants already and if we can just get the agency to actually stick a

stake in the ground and say, "This what you need to do," then it would open the door for a lot of plant-based pharmaceuticals.

Goldner: I'm not specifically familiar with some of these regulations. I'd just say, generically, as an economist, that I'd prefer to see something that is economics-based on benefit/cost analysis. We have an ORACBA within the department in one of my sister offices—the Office of Risk Assessment and Cost/Benefit Analysis—which reviews regulatory procedures within the department and is led by an economist. So, I'm going to be provincial and declare that as my generic interest.