Panel Discussion and Q&A

Moderator:
Anthony M. Shelton
Cornell University
Ithaca, NY

Panelists:
Henry Miller
Hoover Institution
Stanford, CA

Mark Nelson
Grocery Manufacturers of America
Washington, DC

Henry Miller: I'm sure you are all familiar with the adage that the three most important factors in the value of real estate are location, location and location. Well the equivalent in public policy is context, context and context. Unfortunately, public-policy discussion groups, like Pew, the misnamed Center for Science in the Public Interest, Greenpeace, the Union of Concerned Scientists and other anti-technology groups consistently omit the context that is essential for judging and crafting public policy toward recombinant DNA technology and products from it. Contrary to these organizations' claims that they are nonpartisan and agnostic and honest brokers about biotech, in fact their workshops, conferences and publications invariably show a pervasive risk-averse and pro-regulatory bias and they attempt to create a presumption of genuine controversy where none exists. Mr. Rodemeyer's comments earlier seemed very moderate, so you have to scratch beneath the surface a little bit to find the disingenuousness. He spoke about unique requirements for recombinant-DNA modified organisms. And he mentioned animals and forestry. In fact, as Roger Beachy pointed out several times, it's not the technology that should serve as the trigger for regulation, rather it's the intrinsic risks imposed by the host organism and any new traits that have been introduced, whatever the technology that's used. Genetically improved trees and forestry are not, in effect, new. Who here would say that the forests that were planted and maintained by companies like Weyerhaeuser and Georgia Pacific are not in fact genetically engineered. Animals are a good example. There are animals that are natural mutants about which we might be concerned. There is a natural mutant of the rat, that's about five times larger than normal. Regulators

aren't interested in that, but they are interested in innocuous organisms that have, say, a marker gene introduced with recombinant DNA techniques. Often on bulletin boards I see advertisements for animals that have resulted from a cross between a timber wolf and a German shepherd. Some of these are F2 generation and three-quarters timber wolf and one-quarter shepherd, and these aren't regulated. Perhaps they should be—they have potentially worrisome characteristics. What's the motive for these misrepresentations, this lack of context about biotech and about process versus product as a trigger for regulation? Activists understand that over-regulation is an effective tool to inhibit innovation and to slow the diffusion of even a superior technology or product of which they disapprove, and they've had modest success. You've heard how expensive and debilitating our current regulatory schemes are.

What is the essential context that I'm referring to? It has to do with food safety so I won't belabor this, but, as you are aware, with the exception of wild berries, wild mushrooms, wild game and fish and shellfish, virtually all of the organisms—plants, animals, microorganisms—in our food supply have been modified by one genetic technique or another, and in crude and sometimes unpredictable ways. Second, because recombinant DNA techniques are more precise than their predecessors, biotech-derived plants and foods, including those making PMPs and other industrial materials, are likely to be even more safe, more predictable than other products. Yet, they alone are much more highly regulated. And so we've ended up with a regulatory process in which there is an inverse relationship between risk and the degree of regulation, which makes absolutely no sense. Third, the FDA does not normally perform safety determinations on new food varieties, but primarily conducts surveillance of marketed foods and takes action if any are found to be adulterated or misbranded. And lastly, unwarranted excessive regulation discourages innovation, imposes costs that are passed along to the consumer and are a disproportionate burden on smaller companies and academics. Again, Roger Beachy talked about how debilitating regulation and its expense and its distraction have been to research in the public sector. Nina Federoff made that point repeatedly in her excellent book, *Mendel in the Kitchen*. In both flagrant and subtle ways, anti-biotech lobbyists and propagandists—that's really what they are—continue to perpetuate various manifestations of the big lie. That is, that agbiotech is untested, unproven and unregulated. Their agenda is not to advance environmental protection or public health, but really to arrogate control over what R&D can be done and which products and technologies can have access to the market place. You heard a very moderate sounding presentation from Mike Rodemeyer. Don't take my word for it. Go to Google and put in my name and Pew or my name and Pew and biotech and CSPI and read the articles. You will get hundreds of links. Some of these articles are peer-reviewed and you can examine them for yourself. Also look at the specious surveys that these organizations have done and the extremely poor, unscholarly quality of the reports they produce and make up your own minds.

Much of the anxiety about the kinds of products that we are concerned with here does not take into account the realities of contemporary agriculture. As you've heard and as you know, gene flow is ubiquitous. Gene transfer is an age-old consideration for farmers and plant biologists. Farmers in North America who grow hundreds of crops, virtually all of

which have been genetically improved in some way, have meticulously developed strategies for preventing cross-contamination in the field, when and if it is necessary. The demands by some, including parts of the food industry, for food plants to be largely off limits for biopharming are really quite absurd. At the same time that such a prohibition would offer minimal incremental safety, it would severely stigmatize the technology and push the development of costs of biopharm products into the stratosphere, limiting development to very high value-added substances and inflating the ultimate costs to the consumer of those few products that do reach the marketplace. USDA's approach to regulation of biopharm crops, which, by the way, largely follows the demands of the food industry and the radical environmental lobby, is unscientific and debilitating: purely technique-based, process-based triggers to regulation. Typical of federal agencies whose approach to the regulation of recombinant-DNA-modified plant varieties in general, USDA's rules impose highly prescriptive design standards that don't take into account the actual risks of a given situation, but mindlessly dictate one-size-fits-all requirements. Moreover, the regulators exclude the establishment of tolerance levels although, ironically, regulators have established tolerances for unwanted contaminants in food, including fungal toxins, insect parts and rodent droppings. Although we do have long experience in segregating crops when necessary, human error is inevitable so it's reasonable to ask what the likelihood is of consumers sustaining injury in a worse-case scenario in which biopharm crops enter the food supply. Well, consider that, first, the active substance would have to be present in the final food product, say tofu or a salad dressing made with soybean oil, or in corn chips, at sufficient levels to exert an adverse effect, the result either of direct toxicity or allergy. But as with the ProdiGene incident several years ago in which biopharm corn stalks that contaminated a subsequent crop of soy, in most instances there would likely be a huge dilution effect. For example in the ProdiGene case, miniscule amounts of biopharm corn stalks and leaves were pulled into a massive soybean harvest. Second, the active agent would need to survive milling and other processing and cooking. Third, it would need to be orally active, as, by the way, the ProdiGene product was unlikely to be. And in any case it was simply a vaccine protein that was intended for veterinary use. So the probability that all of these events would occur is extremely low.

The regulatory obstacles to many of these products are going to be prodigious. Having spent 15 years as a federal regulator, I can tell you that regulators are suspicious of innovation, they are uncomfortable with new technology and the easiest way to cope with it is simply to stall, not to approve much, to ask for more and more studies and to be extremely, conservative.

Tony Shelton: Okay. That will certainly open up some questions. I was just looking over the NABC theme, which is providing an open forum for exploring issues in agricultural biotechnology, so we will certainly have an open forum on that. Mark?

Mark Nelson: There are some people in the food industry who, if PMP plants were planted, grown, harvested and processed on the moon, that would be fine with them, but the position of the Grocery Manufacturers of America (GMA) is a little more nuanced than

that, and I will return to that. GMA is the largest food-, beverage- and consumer-products association in the world. Our 120 members have a combined sales of about $500 billion a year, with two and a half million employees in all fifty states. Somewhat above 95% of supermarket products are from GMA's members. The earlier talks in the plenary session and then what we heard from the two previous speakers, I found fascinating—intellectually very stimulating. You folks doing this every day, you reach these goals, you make these accomplishments, it has to be incredibly satisfying and no doubt I will be a beneficiary from some of these products in the future. But the concern the food industry has with this is the simple fact of adulteration. It may not be a safety issue, but while we do like to talk with our consumers, we don't like to have conversations like: "About that cancer drug in your corn flakes? Don't worry, the FDA says its *de minimis*." Our concern is not based on marketplace issues as was mentioned earlier, *e.g.* that company A would say company B's product is contaminated. There are people like that in the food industry—as there are in any industry—but most don't engage in *schadenfreude* because they know it could happen to them. They have a common approach to make sure that the food supply continues to be safe. It comes down to our pocketbooks. If you have an adulteration, it will cost a lot of money to deal with it, particularly where a safety evaluation in the food has not actually been done yet. That's why, as an organization, we have asked FDA on more than one occasion for more regulation. Now I know that's different from what Henry was just talking about and what we heard earlier, but again it depends on context. As I understood it, your concern and your frustration was with regulation of transgenic events and it makes a lot of sense to me that if it's the same event or the same gene, why do we have to reinvent the wheel every single time. We are *Homo sapiens*, we should be able to learn from experience. But, in our situation—in the food industry—we want to make sure that the food supply is safe, and, currently, as these PMPs are being reviewed for field tests there is no full safety evaluation of the implications if these are commingled in the food supply. The FDA in its own documents and proposals for various guidelines and regulations has indicated that as these field tests increase in number, the probability of commingling also is likely to increase. Dr. Davies mentioned some very compelling points about why there is increasing pressure to make pharmaceutical proteins in plants. It makes a lot of sense. And while the economics would suggest that we are not going to rush to tobacco any time soon, the fact of the matter is we do know a lot more about some of the food crops and have experience in handling and managing them, and so they make perfect vehicles. Dr. Korban mentioned oral vaccines with fresh tomatoes and carrots, providing a new take on the concept of health-food stores. But regulations already exist for those, which would be considered drug-delivery vehicles and they would have to be separated; they wouldn't be in our food supply. So what have we asked FDA to do to help maintain the safety of the food supply, to allow PMPs to deliver benefits but at the same time make sure that the food supply is maintained in a safe way? We have asked for a mandatory food-safety review for these. Currently, a PMP would be evaluated by USDA by the APHIS Biotechnology Regulatory Services and it would deal with the center in the Food and Drug Administration responsible for drugs. [audio lost] Specifically, we have asked FDA to evaluate the compound, look at the quantity in the food, the impact of the

food in the diet, look at the possibility that it would be changed or degraded or denatured by processing and then assess it against existing regulations. Some of these proteins may in fact already be approved food additives or GRAS[1] substances, in which case if they got into the food supply they wouldn't be a problem, unless they were in foods that they are not supposed to be in or if they were at levels that were beyond the regulatory limits. But those probably are few and far between. If it is not a GRAS substance or a food additive then by definition it's an adulterant and what we have asked then is for FDA to set up reasonable approximate standards. If a crop contains this compound at X level, at 10 or 15% and there is no health problem, then perhaps you just need a simple Class-1 recall. On the other hand, if the amount in the food supply is at a dangerous level then there should be a Class-3 recall if it's in the food supply through commingling. Then that food-safety assessment should be used to inform the permit requirements. So perhaps there are different levels of physical separation or biological separation. The gene-control cascade concepts we heard of earlier would probably be something that would be very helpful to limit that. Dedicated equipment, trained employees with standard protocols are already being asked for by USDA and those would make perfect sense in our estimation as well. So, as I said earlier, some people in the food industry would like to see these things grown on the moon, but we recognize that that's not feasible but we do think that we can use our experience and our knowledge and existing regulations to take a much more reasoned and nuanced approach to help the biotechnology industry—and particularly the PMP part—develop and also maintain a safe food supply.

Shelton: Are there questions from the audience or questions that panelists would like to ask each other?

Steve Rock (Environmental Protection Agency, Cincinatti, OH): As a research scientist, the definition of "side-effect" was something I didn't think about or didn't want to think about. And I want to ask the panelists to think about what happens if you change your mind. And in terms of what Mark was saying about recalls—we have had recalls. We have had products that we put into the food supply that we decided we didn't want in the food supply and were able to recall at some point—cyclamates, red dye #4. Those things were fairly easy to extract from the process. And I wondered if you all have thought about how easy it would be to extract these from the process? As a scientist in research and development, I don't know anybody who is against innovation. Most of my colleagues in the research world are all for innovation as long as there is a significant probability of getting it right, and when you miss there is some way to correct the error. I spend a lot of my time cleaning up historical contamination on hazardous waste sites, specifically oil and DDT. The oil I'm working with has been in the ground since Rockefeller set up his first refinery, 100+ years ago. And although DDT hasn't been used since the 1960s in the United States, we still find it in food supplies around the world. It's hard to get it back into the bottle once you let it out. And there are other examples from the world of

[1]Generally regarded as safe.

ecology—rabbits in Australia, innocently released into the environment and it's now one of their biggest problems. I am wondering how to make it possible to recall our mistakes, which is why it makes a lot of sense, not to stop progress but to go very, very slowly. Twenty years in terms of technology innovation, seems like a huge amount of time. We run on a time scale where a long-term investment is 3 months. And that's crazy. We have to be thinking on at least a generational, if not a geological, time scale because that's what we have to live with. How do you put the genie back in the bottle and what do you do when you change your mind?

Miller: We just had a good example. I hope I don't understate it when I say that that's why EPA may be the worst regulatory agency in the history of the world. I gave the example of the ice-minus fiasco[2]. Nobody, I think, is arguing that there shouldn't be any regulation. What we are arguing is that it should make sense, it should be based on science and that the triggers for regulation should be risk-based. I'll give you an example. About 20 to 30 years ago, a new variety of wheat was developed in a number of countries, the United States, the Soviet Union, Germany and so on. This construction contained all the chromosomes, all of the genes of bread wheat plus all of the genes of wild quackgrass or couch grass. So it contained the entire genome of red wheat and tens of thousands of new genes that were introduced who knew how, who knew with what effect. Nobody, least of all, EPA or other regulators or the anti-biotech activists asked whether the introduction of these genes from a wild grass could make the plant more weed-like, more aggressive in the field, nobody asked whether the gene products of any of these tens of thousands of new genes could be toxic or allergenic in any way. And so these went into the field, they went to large-scale, they went to commercial scale, they went into the food supply with no oversight and not a whimper. But now if someone were to move a single gene of couch grass into *Triticum* using recombinant DNA techniques—even a housekeeping enzyme of some sort—it would bring down this massive, debilitating, very expensive, very lengthy regulatory process from EPA and/or USDA and/or FDA, adding tens of millions of dollars to the regulatory process. This is irreconcilable scientifically. It's preposterous. Roger and I are arguing, not for the absence of regulation—that it be rolled back—but that it be rationalized, that it make some scientific sense.

Shelton: I wonder if the previous speakers, Davies and Korban, who commented on that technology, have any questions for the panel members.

Maelor Davies: Thank you. With the *Nicotiana* system—we don't call it tobacco because we are using other species, we are moving away from conventional crops—we hope to facilitate further development of PMPs with a plant that cannot cross-pollinate with the existing related crop, conventional tobacco. It will be different enough to represent a unique plant variety for PMPs. My hope is that, as we do that, if those companies—and we do work with all the companies that have significant activity now in tobacco-based

[2]See page 53

PMP technology—can also advance our situation we may be able to prototype, as it were, a larger-scale commercial PMP in the field setting. In time then, that may enable companies with food-plant-based PMP technologies to advance as well. So, we hope to facilitate the whole thing almost by circumventing this issue for the time being. We'll just have to see how that goes and how that develops.

I hope that I didn't, in any way, cast any negative perspective on USDA. I think USDA-APHIS-BRS is doing what it has to do. It has to go carefully and check out every detail of this whole PMP situation. But what I did point out is that those regulations—such as they are today—are probably not commercially workable. Temporary stringency is necessary to build up a comfort level, and as experience is gained in the field we will look at gene flow. At our center, we are designing specific experiments to look at these issues over the next few years to examine how effective is the mandated containment, what is the gene-flow situation and other such issues. My hope is that eventually things can lighten up significantly because the regulatory system needs to be one that companies can work with economically, commercially successfully, and that growers can afford to implement and safely and routinely comply with, without excessive cost.

Miller: One set of precedents, although they are not perfect for PMPs, are such pharmaceuticals as morphine, codeine and even Metamucil®, which come from plants and with which regulators and industry and consumers have a great deal of experience.

Schuyler Korban: I would echo the comments just made. We do not object to the regulatory processes as long as they are based on sound science and are realistic. Vaccines are produced in eggs or in yeast cells, both of which are part of our food supply. We have to similarly isolate those food crops that are used as vehicles for producing subunit vaccines or other therapeutic proteins. And we heard of some of the ways of reducing or minimizing or essentially eliminating their presence. However, there is no such thing as 100% safety in anything that we deal with. With any of the food or environmental issues that we are trying to resolve, there is no such thing as a 100% guarantee for anything. We can think in terms of minimizing the risk and that's being realistic. Our expectations must be sound, science-based and realistic.

Nelson: I agree that the regulations need to be based on sound science and they need to be proportional. That's why we are suggesting that permit requirements be based on the potential risk if the product were to get into the food supply. And I agree with that no system is 100% perfect. That's why we are asking that safety evaluations be done ahead of time so that we understand what the agencies' actions will be ahead of time, so that we can work with them. We want to avoid another StarLink™ situation, which ended up not being a safety issue but an adulteration issue that caused hundreds of millions of dollars in recall costs and the food safety system took a dent. And we have had huge decline in corn exports because of that exercise and that experience. So, we would like to make sure that it's proportional and know ahead of time what it is we are going to do. We're smart enough to do that. We're smart enough to make that kind of assessment so we aren't scrambling around like a bunch of chickens.

Shelton: Speaking of chickens and eggs and their getting into the food system—if the plants are not going to be grown on the moon, like you said, but if they were grown in the field like tobacco would that be something that GMA would support—the idea of producing PMP's in tobacco?

Nelson: Well it's a non-food crop, but clearly the smoking and chewing tobacco industry has certain concerns about GMOs, I guess. Yeah, our preference would be for non-food crops. But, we know that that is not always going to be economically or biologically feasible. We are asking that if it is grown in a food crop, that the assessment is done and then appropriate controls be put in place to manage it so that we do minimize entry into the food supply.

Shelton: GMA has a tremendous amount of clout. The decisions that you make are really going to affect PMPs in the future. Have you given guidelines in terms of crops that would be acceptable and not acceptable?

Nelson: No we haven't gotten into that detail because we are not experts on particular crops. For the primary food crops—wheat, corn, soy, rice—field tests are limited at this point. We are concerned that management controls be in place. We are seeing that in some of the permit requirements now coming out for such field trials; they do seem to be stronger. They emphasize greater separation, better training, and so on, to make sure that they are contained.

Gregory Jaffe (Center for Science in the Public Interest, Washington, DC): Going back 10 to 15 years, a combination of small and large multinational companies did a lot of the research on the GM plants that eventually were commercialized. In the bio-pharming/vaccine area some very small companies are involved and the multinational pharmaceutical companies are not. Why is that? Why are the big, multinational companies that are producing these kinds of drugs and biologics, not doing research and field trials in this area? Also, will the success of these products need those companies to get involved as partners or to assist in bringing the products to market? I'm sort of curious as to why they haven't become involved. The speakers listed all the benefits of this type of production model, so why aren't they dabbling in this?

Korban: It is surprising, considering the advantages of using plants for developing vaccines, not only from a production standpoint but also from a delivery standpoint. But, the way I understand it is that the vaccine industry is not very big and the margin of profit is not very high. As a result, interest is not strong at this point. However, with the recognition that they need to move away from animal-source contamination of biopharmaceutical products I think you will see expressions of interest, including from Monsanto. The big pharmaceutical companies are not partnering—especially with university researchers—to push this further. If major investment in this technology does not come along, it will fail eventually.

Davies: I would certainly concur with that. We've thought about this for a number of years and we've talked to the industry both on the ag side and the pharma side. Let me hit on a couple of points. First of all, the technologies for expression in plants were initiated mostly by university faculty who then started companies. In other words, the big guys didn't have the technologies. But that isn't the ultimate answer because then you could ask why doesn't big pharma or big ag invest in or acquire them. We were very encouraged early in 2005 to get a visit at our facility by a major pharma company. I'm not at liberty to say who it was, but that company is becoming concerned about the pressure on protein production and is beginning to scout out and explore the plant-based technologies. But why has it taken so long to get to this point? It's a business issue. It has to deal with big ag companies and big pharma having their particular strategies. In the case of big ag, not owning the drugs means that they don't see how they would make sufficient money out of it ultimately. On the big pharma side, they tend to be very conservative and very cautious about even new drug technologies. They are waiting for university spin-off drug companies to prove that their particular vaccine or whatever is a real winner and then they will come in and acquire it. So it has to do with business play and market fit and corporate-strategy fit and similar issues. I think that increasing demands for proteins will eventually change this paradigm and make big pharma pay attention to these alternative platforms.

Tom Reddick (Global Environmental Ethics Council, Clayton MO): Glycosylation was mentioned. I heard that hamster ovaries are used for mammalian cell lines to create proteins that will glycosylate properly. Is that a technical hurdle that lies in the future? Will the FDA balk at approving a plant system for efficacy if it doesn't glycosylate like a hamster?

Davies: Probably yes to all of the above. There are certain modifications to proteins that animal cells do, including glycosylation—attachment of carbohydrates—that plants either don't do or do differently. This is a challenge that the microbial fermentation world has also been somewhat limited by and that's why mammalian systems are used to produce mammalian protein drugs. Some protein drugs will not be suitable for plant-based production. They would be more suitable for mammalian cells in culture or whatever. If it turns out that the non-protein component, the carbohydrate substituent, is not essential for function, the plant-made protein with the necessary biological function but without the substituents might be regarded as a new drug and need to be registered as a new synthetic. We'll see how those things play out in time. We don't know the complete portfolio of products that the PMP companies are looking at, but we certainly get the sense that they are focusing on the ones for which this will not be an issue. Dr. Beachy has alluded to some work that is going on to actually modify the plant so that its production of the substituent groups, like these carbohydrates, would be so-called "humanized." Probably quite a lot remains to be done for that to be successful because differences in the carbohydrates are quite complex.

William Goldner (USDA Small Business Innovation Research Program, Washington, DC): If you produce industrial enzymes or industrial proteins in crop plants are the same issues faced as for pharmaceutical proteins?

Nelson: Yes. We have raised the same concerns with the FDA, not just with reference to PMPs but also plant-made industrial chemicals. The same issues apply, but it would be an adulterant. The safety issues may not be as great, but we have asked that it be looked at.

Miller: Once again, it's useful to look for applicable precedents and a very good one is rape seed. The original rape seed oil was highly toxic. It was used as an industrial lubricant; it couldn't be used as a cooking oil because it was extremely toxic. Plant breeders came up with what is called a "double-low" variety, low in erucic acid and glucosinolates. Both varieties are still grown—one to produce industrial lubricants, one to produce canola oil—and we've established means for keeping them segregated. We've established tolerances for the toxins in food. Again, it's extremely useful and important to look for applicable precedents to figure out where we need to go and what makes sense.

Milt Zaitlin (Cornell University, Ithaca, NY). I've seen in the literature that some plant-based vaccines do elicit antibodies, but why don't other proteins that we eat also elicit antibody formation? I guess people get allergenic responses to wheat proteins and so forth, but what characteristics would lead you to believe that a transgene product would be more immunogenic than normal proteins that we eat?

Korban: You could ask the same question of any vaccine that you take, especially when you are dealing with subunit vaccines. These are antigens that produce specific antibodies. All we are doing when we use plants to produce such an antigen is to provide a vehicle for production. Now you can purify that antigen if you so desire and introduce it intramuscularly. That's what the tobacco system would be used for. Or, you can strictly consume it orally without purification in that plant system.

Zaitlin: I don't think you've answered my question. We're talking about an oral route. We're not talking about injections.

Korban: The way to think about it is that with the antigen administered orally, it's inducing specific antibodies that provide protection. Now, there are other proteins within the plant system that we ingest that are used to provide nutrition and do not induce antibodies except if a protein is allergenic and that's when you have a concern over ingestion of this particular protein. I don't know if I've answered your question correctly.

Elizabeth Hood (Arkansas State University, Jonesboro, AR): At ProdiGene we did some animal experiments to address this issue. There's a distinction between whether or not you make antibodies against a protein that you ingest vs. having an allergic reaction. The rabbits had already raised their own antibodies to orally consumed corn-seed proteins that were naturally there. So, we made our own antibodies for testing on pre-screened rabbits that did not already have these antibodies in their blood serum. There's been a

lot of misuse of the term "immunogenic response" with respect to food based proteins. We make a lot of antibodies to things that we ingest; they are not all allergic reactions. The mechanism of making antibodies against an orally consumed antigen is a normal response to proteins that we ingest. We make antibodies to lots of things that we ingest, we just don't always have allergic reactions to them.