
Session 3-1: The Regulatory Process and Technology Access for Specialty Crops

Q&A

MODERATOR: DAVID BALTENSPERGER

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Alan McHughen (University of California-Riverside, Riverside). Patricia, thank you very much for your overview of the Canadian situation. I'm curious to know how many genetically engineered plants cultivated in Canada are not considered PNTs¹, and so didn't go through your approval system?

Patricia McAllister: There are none.

McHughen: Then, I'm confused about what your definition of a novel plant is. With *Bt* corn in the United States, of course we use event by event. It sounds like that's what you do in Canada as well, which would seem to be contrary to the PNT concept.

McAllister: At this point, all genetically engineered products that have been put forward have met the definition of a plant with a novel trait. The ones we have that are more unique are the ones that we regulate that the US wouldn't regulate. For instance, turf grass without question would have hit a novelty trigger in Canada. And we have sunflowers, lentils and wheat that are herbicide tolerant that were not developed through genetic engineering, and those ones are regulated in Canada as PNTs. So, we capture a broader number of products.

¹Plants with novel traits.

McHughen: Right, you capture more in terms of the mutagenesis and non-recombinant things. I recognize that and appreciate that, but I also thought that the point of the plant-with-novel-trait product trigger was so that once you get an event through—a *Bt* corn, for example—the next *Bt*-corn event would not be considered novel. How do you then define the second and third and subsequent *Bt*-corn varieties as being novel?

McAllister: There is certainly a lot of talk about where it will go, but at this point each one is triggering the regulations as it comes through.

McHughen: Is there something in the trait? I'm confused about that now because I thought that the system was developed in Canada so that subsequent things that don't have new traits would not be captured. What is the scientific basis for a new trait that is the trigger?

McAllister: I am unable to answer that question. I have been with this group since September and my job has mostly been issues management. A few things—like alfalfa—have created havoc for us. I was not part of the development of these regulations and I simply work with what we are given. But, believe me, our major players are frequently asking us, *When are you going to the “me too” products—when you’ve already looked at a trait?* They certainly can go into conventional breeding. We don't have to approve individual varieties, but, if you are modifying your event, we are still going back and looking at it again.

Julie Svetlik (Texas A&M AgriLife Research, College Station): I think Patricia already answered this question for me—thank you—so the question is for the US agencies. Assuming a plant or product has cleared the regulatory process in your agency and has been authorized and has entered the market, are there procedures in place at your agency to reevaluate status if new data come out that indicate that the plant or the product is not safe for humans or the environment?

David Heron: I'll go first since ours looks like once our hands are off, they are always off—but if new evidence demonstrates a risk as a plant pest, then we do have the authority to bring it back under the regulation. We have not seen that yet.

Robert Merker: We have seen a number of instances in which new data have been brought back to us at some point or other, but it has always been data that do not change the final conclusion of safety.

Chris Wozniak: Our statute is a bit different. FIFRA is a licensing statute, so as long as you want to distribute, sell or use that pesticide in the United States, then you are under the license, meaning you pay an annual maintenance fee, you have to supply reports on sales figures, etc. But you are also beholden to a clause referred to as “6(a)(2),” where, if there are any adverse effects—and that is determined by the agency not by the individual so much—anything unusual has to be reported to the agency in a timely manner and we

maintain a database of what we call “6(a)(2) events” and determine whether they require follow up. In addition to that, because it is a license, all of the registrations have a term of expiration and these will vary. For example, with the *Bt*s, part of it depends on the durability of the product. The product seen as being durable in terms of resistance to insects might get a 10- or 12-year registration. If it’s a single-trait product, it’s more likely to get a 3- or 4-year registration and, at those times, they are reassessed and they may enter what is called a re-registration or re-review process, where people basically look at the literature and look at what is known, and anything else that may have come up since the initial registration and then make a determination of whether data are required. We have a process that is called “data calling,” where, if something comes up, we can request that information.

Robert Wager (Vancouver Island University, Nanaimo): Each of you, in your own way, has mentioned that GM crops and non-GM crops with similar traits are regulated roughly the same way. My question goes to Cry proteins, and it appears to be that that’s not always the case where you have significant regulatory requirements for a GM crop with a particular Cry protein engineered into it, whereas I don’t seem to see—perhaps I’m wrong on this—any real regulations involving using the *in vivo* whole bacterium expressing the same proteins and I’d like to understand if, in fact, that is true and, if so, why?

Wozniak: If you are speaking in terms of using either a spore or spore-plus-cell prep as a biopesticide—yeah, we certainly regulate those. We have both engineered and non-engineered forms of *Bt* as well as dozens of other microbes for use as insecticides, nematicides and even some as herbicides. So I’m not sure why you are picking on *Bt*. Any microbial agent, whether it’s a virus, bacteriophage, protozoan, alga or fungus, that has a pesticidal claim associated with it—in other words preventing, destroying or repelling some disease or pest—is a pesticide under our law. I think, at last count, we have 97 active ingredients and from those stem hundreds of products.

McAllister: From the Canadian perspective, those would not be regulated by the Canadian Food Inspection Agency, but would be regulated through Health Canada’s Pest Management Regulatory Agency.

Bob Avant (Texas AgriLife Research, College Station): Recently, the USDA said they are going to go into a full blown EIS evaluation of new genetically engineered events, and I would like to hear some conversation: does that really change much about what we are doing? Is it going to delay the process? The conventional wisdom is, anytime an EIS is required it costs millions of dollars, it takes years to do and it’s a good way of delaying things. Does it represent any change or is it just another hurdle we are going to have to cross to get down the path?

Heron: As far as whether everything is going to require an EIS, no it won’t. An EIS, for those of you unfamiliar, I referred to as environmental assessments under NEPA,

the National Environmental Policy Act. If an agency cannot come to a finding of “no significant impact on the environment” when they do an environmental assessment, if they want to proceed with considering the action, then they can go to an environmental impact statement, which is a more involved process and, like the environmental assessment, has public involvement. The agency has interaction with the public throughout the process. But, the fact that these are now being open for public comment on the process called “scoping” to see the extent of the environmental impact statement, it does not mean that it is going to happen for all. These were seen as issues that are very closely related and it would be difficult to consider them separately. The decision on whether federal agencies choose environmental impact statements or environmental assessments is rather complex. It involves legal reviews with the department, interaction with the Council on Environmental Quality, which is a lighthouse that takes a look at NEPA and its obligations to federal agencies. Maybe that’s a long way of saying that no, this is not going to be the standard and yes, it is a more involved process.

Bill McCutchen (Texas AgriLife Research, College Station): A scenario here for you to think about. What would be the steps if, let’s say, a spinoff company from Texas A&M or another university were put in place for a specialty crop whereby—and I know this is a big “if”—if we had freedom to operate and we had a license for a previously approved herbicide and or *Bt* gene and we wanted to put that into onions or another vegetable, would we be required to go through the entire process again in terms of digestibility, allergenicity? Because, a big expense is the non-target organism piece—doing the types of tests that require, as you know, a lot of work and money. So, would it be possible to license from Monsanto or DuPont, let’s say a spinoff company for our university of a previously approved gene for herbicide and insect resistance and assuming we had freedom to operate for agrotransformation, *etc.*, what would be required?

Heron: We regulate organisms. We don’t regulate genes. Congress set out the definition of a plant pest, so that sets the parameters. When we are making a decision for non-regulated status it’s for the organism. It’s not for the gene. The information we may have in looking at a gene in another organism may inform our review subsequently but that would not mean that you don’t come in if you take a *Bt* or herbicide tolerance cassette and put it in onion instead of cotton. The onion would still come through us.

McCutchen: I understand that. I’ve been through this process many times in a former life, but if this has already gone through tox tests, non-target organisms, from a scientific standpoint—I understand there is law and regulation—why can’t we get together and streamline some of these things and help our producers help themselves? Can we work across agencies and with institutes to develop new products that aren’t so new but are in different vehicles if you will?

McAllister: From the Canadian perspective, if we are more familiar with things it can make it easier. It’s how you can communicate your story, but, in reality, you would need

to speak directly to our specific assessment group. If it's in a new plant, it's definitely going to be assessed as a new product, but whether you'd have to redo the allergenicity data and the other toxicity data for genes that we are very familiar with, that would require a very specific discussion.

Wozniak: Where it truly is the same gene and not some modification or a similar type gene, there is a process called "data compensation" where you can compensate the company that originally submitted supporting data. So that's one avenue. In terms of the environmental side of the equation where you are looking at non-target effects, if you are changing the exposure scenario then it is likely you are going to have to look at some data generation for specific pests. In other words, the beneficial insects you choose that might be representative of a corn field in Iowa may not be the same as that represented by an onion in Texas. So that would be up to the risk assessor to determine what types of studies would have to be generated *de novo* and which ones could be bridged. We do occasionally bridge data, particularly so with microbial agents, but certainly it's plausible with some of the PIPs. Now, as for the larger question in getting away from event by event transformation even within the same species, you can take a PIP that's been registered in field corn and do the appropriate crosses, you know, typical sexual, traditional breeding crosses, move it into popcorn, and you are covered as far as the tolerance goes and all that. However, one of the arguments that has been made—and I'm not saying I agree with it 100 per cent—but if you generate a new event through transgenesis, either through *Agrobacterium* or the gene gun or whatever your mechanism, then your position within the genome, as far as where your transgene inserts, can influence the pattern of gene expression. So, in our case, one of the things that we look at relative to non-target effects but also just for the overall accumulation of your pesticidal substance, which needs to be recorded on a confidential statement, that requires an assessment. You know, is it identical just because you used the same promoter and the same open reading frame and the same termination sequence if it's in two different crops or even within the same crop but it's in two different positions? That's the crux of the argument. At what point do you say, *Well, we've seen this enough and the likelihood of that happening is small enough*, I think that, in some respects, is what we are moving toward, but as far as going between different species, like, say, onion and corn, that's a larger question.

Merker: I defer to EPA on pesticide issues, but, for food and feed safety, if we've seen the proteins before, essentially we've seen the proteins before. The allergenicity assessment and the assessment for toxicity would be the same and could be done either by incorporation by reference or by summarizing what information we had seen before and where we could find it. Certainly we wouldn't make somebody do that over again, and, as a for instance, if you were dealing with our favorite antibiotic resistance marker, NPTII, we actually approved that as a food additive, and even if you were using it in one of the crops for which it wasn't approved, if you pointed us to that approval, certainly we would want to know the specifics of how it got integrated, but the safety of the protein could be referred back to our regulation.

Wozniak: One thing I want to clarify—just to make sure—there is a difference between what's ruled under FFDCA like the tolerance action, versus what's under FIFRA, which would cover, for example, non-target effects but also human health effects. So, for example, if you are working with Cry1Ac as your insecticidal protein and it's already covered by a tolerance, then you don't have to redo the studies that are associated with that tolerance. It could be an oral tox test, allergenicity, *etc.* However, on the FIFRA side, if the concern is more about exposure of non-targets then that is where the data compensation would come in—where you would likely pay another company to utilize their previously submitted and accepted data.

Charles Rinerson (Texas AgriLife Research, College Station): Dr. Merker, the basis for the consultation and regulation you were talking about earlier was based on the FD&C Act. Do you see a different consultation process or considerations if the plant or product were regulated under the DSHEA Act²?

Merker: Certainly, if it comes in for something in a dietary supplement, and there has been a history of exactly one of those coming in. It may fit the criteria for consideration as a new dietary ingredient and it would be the substance going into the dietary supplement that would need to be looked at, not necessarily the whole crop.

Roger Beachy (Global Institute for Food Security, Saskatoon): I'd like to take us back just a bit—and maybe this is too big a question to answer today—but, in 1987, when the coordinated framework was developed, it was expected that there would be a full reexamination of the coordinated framework in some period of time, 7 to 10 years, and that we would learn from those 7 to 10 years about what to go forward with. In fact, some of the original challenges were to try to eliminate regulations based on what we'd learned in the first 10 years. We haven't done that yet. We've learned more about what to regulate, what we think we know about to regulate, but in fact, regulation is not simplified, it's made more difficult because we keep adding more on each time someone raises a possibility of potential damage or danger. When is it time to re-evaluate the coordinated framework and come up with a new framework? We are now more than 20 years in and we haven't re-evaluated. When is it time to take the learnings of science since 1987 and redo the coordinated framework based upon what we've learned and what we expect to see in the following two or three decades? I ask the question because most of us feel that, given what happened in 1987—and I was involved in that process too—but Nina Fedoroff and others have reminded us that this is the way that we would start, but we expected to deregulate it more fully and make it easier to innovate, and it's not. I do appreciate the learnings and the ability to cross back and go back to old data and restate them. It should help Texas A&M to simplify, but it's still a more expansive program than had been imagined in 1987. Can you help me understand where we might be in 5 or 10 more years?

²Dietary Supplement Health and Education Act.

Merker: I don't think—from FDA's point of view—that it really has changed. I actually think that our 1992 policy is pretty flexible. Certainly, it's a situation where if the developer wants to seek us out they can and we are available. And the issues are going to be the same: safety and nutrition. As long as those get covered we are happy to consider things. We actually didn't think we would be doing this for this long, but the developers seem to want it, I think mainly for international trade issues, and the public seems to want it as well.

Heron: Yeah, that's an interesting point because, actually in 1992, OSTP³ put out a second document that was actually calling for what you are saying here Roger, to dial it back wherever possible. What I have seen is that unless there is a sustained push in a certain direction it doesn't happen, so the *status quo* stays in place. And so, at the regulatory agencies, we try to run the mousetrap as best we can whether the mousetrap itself has a faulty design, that has to come from outside. I mean, this administration with the Holdren memo, has restated the principles of the Reagan administration. But, in terms of what it actually means in practice—and this is where the distinction between what is in the law and what is placed in regulation and how that works—you can see now that this whole premise of presumed innocence of things developed through genetic engineering has been turned on its head, and so now we are trying to prove a lack of harm, which we all know is impossible to do.

Wozniak: Certainly, I understand your frustration with the lack of change. I think Dave Heron makes an excellent point though, in that it is the actual practice of what is performed, in terms of regulation or deregulation or consultation, depending on the agency. But, in terms of the coordinated framework, I don't think it's a bad idea to reassess that. One of the decisions that was made was to use existing statutes to cover the bases and I'm not going to voice an opinion one way or the other on whether that was a smart idea, but what I will say is that some of the changes that you are talking about require legislative action and have to be done on Capitol Hill, not at EPA or APHIS or FDA, unfortunately. And I think that's part of the frustration, but, again, Dave's point: those changes require forward-thinking people who aren't afraid to take some risk and perhaps some backlash from the public in terms of making some bold moves. Now, one of the things that we have heard about—and it's very obvious to everyone in this room—the lawsuits, for example, that APHIS has had to endure over these last years are always part of the battle. If you try to be progressive and say, *Well, we've seen this enough we don't really need to regulate this*, there are going to be a whole bunch of people on the other side who say, *Oh yes you do*. The Federal Register notices get 50,000 to 60,000 comments, etc. But I think you are right that it certainly is time to move forward and use some of the familiarity we have with these products such that, even if we do regulate them, we do it a much reduced level—basically you would be more cataloguing them than regulating them. Again, it's going to take somebody with a bold heart who is willing to take a beat-

³Office of Science and Technology Policy.

ing to move that forward. Certainly, there is still the issue—although I don't think it's an insurmountable one—where I talk with a lot of foreign governments and it makes them very nervous to think that we're going to have certain things that aren't really scrutinized properly, but some of the companies also tell me, *Don't worry about that. We'll deal with those individual countries in terms of trade. We'll work around whatever their requirements are.* I want to mention one of the proposals we are considering, or reconsidering, and that is a cisgenic exemption with cisgenics defined a little bit more broadly than perhaps is done in the literature. We are in the early stages of reviving that, which is part of a previous data-requirements rule that never got off the ground a few years back. So, that's one instance where, I think, philosophically, it's a major move for the agency to consider a product of recombinant DNA that doesn't require regulation. It's not going to solve the problem for everybody for sure. Those people who still rely on basic transgenesis with foreign genes—it's not going to help them one iota, except in terms of moving that ball forward and saying, *Here's something where we don't have to be concerned just because it's genetically engineered.*