History

of the

U.S. Food and Drug Administration

Interviewee: James Maryanski

Interviewer: Suzanne Junod

Date: August 18, 2006

Place: Rockville, MD

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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National Library of Medicine
Bethesda, Maryland 20894

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Date: August 18, 2006 Place: FDA History Office

INTERVIEWEE
NAME: James Maryanski

INTERVIEWER
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ADDRESS: FDA History Office

FDA SERVICE DATES: FROM : 1977 TO: 2006 RETIRED? Yes

TITLE: Food Biotech. Specialist
(If retired, title of last FDA position)

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Interview with James Maryanski

August 18, 2006

TAPE 1, SIDE A

SJ: Today is August 18, 2006. We're in the FDA History Office with Mr. Jim Maryanski, the agency's Food Biotech Specialist.

And so we just want to start out by asking how you came to work for FDA, what was your background, where you grew up.

JM: Well, I grew up in Ohio and went to Ohio State University and got a degree in microbiology there, and worked for the Public Health Service for almost three years after that in Cincinnati, Ohio, which later became part of FDA. Then I went to graduate school in microbiology, and after that spent some time at the National Institutes of Health (NIH).

I was hired in 1977 by FDA to be part of the group of scientists who were hired at that time to review the safety of GRAS food ingredients, substances that are generally recognized as safe, (herein referred to as GRAS), because the agency had a mandate to conduct a review of the substances on this list . . .

SJ: After cyclamate and . . .

JM: After cyclamate, this was Nixon's mandate to FDA to look at all the substances on the list because of the studies that had come out on cyclamate.

So I started with FDA in the GRAS Review Branch in 1977, and some of the GRAS petitions that I worked on involved enzymes that were immobilized in columns to make corn sweeteners to produce foods like high-fructose corn syrup -- soft drinks, for example. At that time FDA had a number of petitions from industry to basically start using new technology that's producing these large amounts of corn sweeteners for use in food and food ingredients.

I worked on many other things over several years, including colors in contact lenses and packaging materials and various other kinds of things that FDA reviews as food additives or GRAS food ingredients.

In the early 1980s, FDA began to get some questions about the use of recombinant DNA techniques in applications for food processing. Recombinant DNA techniques refer to the process in molecular biology where scientists in the early 1970s had learned to identify specific genes within the DNA and be able to isolate those genes. They made copies of them in bacteria, and reintroduced those genes, then, into another organism or the same organism. The techniques were able to transfer genes across sexual boundaries, so this was a very new ability that had not existed before. Normally, organisms can exchange their genetic material through sexual processes with closely related organisms. But these were techniques where a gene could be isolated from any source, whether animal, plant, bacterial, viral, and reintroduced into another organism, for example, a food-production microorganism or a food crop.

The scientists, such as Paul Berg, who eventually won a Nobel Prize, who developed these techniques did raise questions about the safety, whether there were any hazards associated. Dr. Berg realized that he was working with a virus that was pathogenic, and he was transferring a gene from that virus into *E. coli*, which is a common intestinal microorganism, so the concern was whether he could be creating organisms that could live in the human GI tract and basically make a new pathogen.

During the 1970's there was a well-known conference that was held by scientists to discuss what should be done in terms of using these techniques in research. And it was through the research experience that was developed that scientists eventually learned how to use the technique safely and learned where the risks were and where they were not.

The NIH, recognizing the concerns that had been raised, established the Recombinant DNA Advisory Committee, which came to be called the RAC, and for a number of years the RAC met regularly and developed guidelines for the use of recombinant DNA techniques in research. Through that experience, from both research and developing the guidelines through the RAC, scientists realized that genes did in fact function the way they were expected to function even though they may be placed in very different organisms, and that there were not unique risks involved with using these techniques.

It was important to evaluate the characteristics of the genes and the organisms that were being used, but that could be done asking the usual kinds of safety questions. There were no concerns raised by the use of these techniques. And that was a very valuable experience in using these techniques.

The first applications commercially were in the pharmaceutical area, as is often the case with techniques in biology. FDA reviewed insulin produced in *E. coli*, where the human gene for insulin was cloned and introduced into *E. coli*, so that insulin could be produced in fermentation instead of being extracted from tissues, as had been the conventional way of doing that. This provided a very reliable, high-quality form of insulin. The big advance was being able to modify a common production organism and being able to produce the insulin, which could be easily purified and have a high-quality controlled system, because that really provided consumers with an important drug. It certainly was a huge technological advance.

That was followed by tissue plasminogen activator (TPA) and hepatitis B vaccine and a number of diagnostics that used recombinant DNA techniques.

FDA had the experience before we even began to think about the use of these techniques in foods, and I think that was very valuable, having that kind of history from the NIH guideline development and FDA's own review of these techniques. We began to be asked questions about, what it meant to put a gene from bacteria into a food crop such as corn or soybeans or tomatoes? Is that a really different, unusual thing to do? And while it is different in the sense that one had not been able to make that kind of transfer before, we knew that, at least in the case of the organisms that had been examined, there were not unique or unusual differences, and genes did perform the way they were expected. In other words, they had the function and the activity they were expected to have.

SJ: And so we're basically looking at whether it's GRAS, whether the products result

in things that were still GRAS, so that's how it became . . . I'm just fascinated that it came under the GRAS rubric, because it makes perfect sense, but it is a very, very different way of conceptualizing GRAS.

JM: That is right to a large extent, because one of the things that we do have in the food area is the GRAS concept under the Food Additives Amendment (1960). The exemption comes from the requirement for pre-market approval for a substance that's added to food or becomes a component of food if it is generally recognized as safe. This is determined by either history of use or by scientific information that is widely available and recognized by experts. This applies to many of the substances that are in foods that are in the grocery store today.

It also gives both the industry and FDA a lot of flexibility to decide which substances are new and different enough that they really warrant the resources to undergo pre-market review and approval by the government before they're used. FDA doesn't want to expend its resources reviewing things that everyone knows are safe. You want to have the ability to catch those things that you're not quite so sure about but probably are safe, which it turns out, most food additives do pass all the tests and become regulated, but it provides that great flexibility. I don't think any country around the world has that. Most people around the world don't understand it. But it's been extremely . . .

SJ: Serves us well.

JM: It has served us extremely well.

When we began to get questions about the use of these techniques -- and I maybe should stop and say that the techniques were called recombinant DNA techniques because they were basically using enzymes to cut DNA and recombine those pieces of the genes with other pieces of DNA. But there have been many other terms that have been applied, such as genetic engineering, gene technology, bioengineering, we have used at FDA. The word biotechnology is often used, but it's a very broad term and usually understood to mean many kinds of biological processes that are used in industrial purposes. And, more recently, modern biotechnology has been used to encompass techniques such as recombinant DNA and other techniques that are more recent. But there is no one word that's very consumer-friendly. It's something that the scientific term of recombinant DNA doesn't make very good press.

SJ: It sounds very technical.

JM: Yes, and there was always a lot of debate. The Europeans didn't like genetic engineering because it . . .

SJ: They still don't.

JM: Or genetic manipulation, for obvious reasons.

SJ: I don't know that it -- to me, the reasons aren't that obvious.

JM: Well, it was associated with some of the eugenic kinds of things. You know, could it be associated with some of those kinds of things?

And so they chose genetic modification, which we always agreed with them that the use of recombinant DNA techniques does make genetically modified organisms. But where we differ is that we think that all methods of changing heritable traits, such as conventional breeding and other methods of transferring genes among organisms, are methods of genetic modification. And so FDA has never really been willing to adopt that as a term that really defines or describes recombinant DNA techniques. And so I think that many countries around the world have adopted genetic modification because the term GM is friendly to the press, and they feel that it's friendlier to consumers, that it sounds softer than some of the other terms such as genetic engineering. So there isn't one good term.

I think for a number of years here at FDA, we used the term biotechnology. Many articles, for example, in the *FDA Consumer* articles, we use genetic engineering and bioengineering, but it's not a crucial point, I think. It's more a matter of just simply understanding that we're talking about . . .

SJ: Nomenclature?

JM: Methods of transferring specific genes, single genes, one, two, or three, a few genes, from one organism to another.

SJ: And was that around the time of, I mean, talk about consumer-friendly terms or consumer-recognized terms -- that's when they came out with the term "Frankenfoods," which certainly got more attention than recombinant DNA, however negative the attention may have been.

JM: Yes, it definitely got more attention. I've always said that if the foods that were developed were really Frankenfoods, my job would have been a whole lot more interesting.

SJ: What were the first ones that you remember approving? The first thing most of us were aware of was StarLink corn, which I'm sure you'll talk about. But what were the first ones? Was it tomato products or . . .

JM: The first one was tomato; it was the Flavr Savr tomato.

But maybe before we talk about that, how about if we talk about some of the concerns that were raised, because why did we get into all of the complex reviews that we have of these products today around the world? Partly because it was new technology, and obviously, FDA, to carry out its public health protection mandate, needs to understand how the changes in the food supply, for example, affect food manufacturing processes. But probably even more importantly in this case, there was tremendous consumer concern, generated primarily through environmental groups, because of the field testing that was going on.

The concerns centered around, originally, questions of transferring genes between different organisms. Was this safe to do, to put a bacterial gene into a plant, for example; to put an animal gene into a plant, where vegetarians found that to be unacceptable? So, there were religious concerns that could be raised about transfers of genes among different organisms, various kinds of ethical concerns people would have, or just simply a gut feeling that this just doesn't sound right. Nature didn't do this; it doesn't seem as if this is what nature does, and therefore maybe this is, you know, there could be some inherent dangers in this, the use of these techniques.

And in that sense, similar to the questions that Paul Berg and other scientists raised in the beginning about the scientific question of "are these techniques safe?", but the public had broader questions that went to ethics and religion and all the kinds of things which we as individuals . . .

SJ: Interfering with creation?

JM: Yes, it could be interfering with creation, it wasn't natural, and so forth.

SJ: But you had to actually know what traits these genes carried. Am I correct? I mean, you wouldn't even know how to begin to manipulate them unless you knew how they were controlled.

JM: That's, of course, true.

SJ: What controls flavor versus size? So there was a fair amount of knowledge going in?

JM: Yes, there was.

SJ: Before anybody would have thought to use that . . . I suppose it was fairly expensive to even gain the knowledge to know how to manipulate them.

JM: That's right.

SJ: They had an interest from the beginning in knowing what they were doing?

JM: That's correct.

SJ: Unlike the earlier food additives at the turn of the century which were straightforward. Formaldehyde was formaldehyde.

JM: Well, for example, the first questions that we got in the food area involved food-processing enzymes, the enzymes that had been used for many years in food production, the enzymes such as the starch-hydrolyzing enzymes that are made to make corn sweeteners. The industry was always interested in,improving their production strains to make them more efficient, more economical, to withstand the heat of processing, acidic

conditions, whatever the conditions are, but to improve those strains. They'd often use chemical mutagenesis to modify the organisms, the production organism, in order to give it enhanced properties.

SJ: But that took time and a fair amount of luck?

JM: A fair amount of luck, and they weren't always stable. There certainly were improvements made that way. We've had cross-breeding in the plant area, in agriculture, for centuries -- well, maybe not centuries, but deliberately for a hundred years. And so there have been many methods of developing improved organisms through altering their genetic background.

But now you had a way to specifically introduce a gene that you knew what its function was, what trait it would confer on the organism that you were going to put it in, and that was an advance in two ways. One, you had that specific knowledge that you were going to use to put in the trait that you wanted. But it also meant there was a wider pool of traits to choose from. You were not restricted to just the close relatives of the organism you're working with, whether it's a microorganism or a plant. You could obtain that gene from any source and introduce it into the food-production microorganism or the food crop.

But the concerns were about whether, in making those changes, you could either introduce a substance that might not be safe for the consumer, it might be a toxin, it might be an allergen, might somehow change the nutritional properties of the food, or it might have some unexpected effect. When you introduce genes into plants, you are in a

sense disrupting the genome, and it is well known that plants undergo various kinds of unexpected effects in normal plant breeding, conventional plant breeding. And plant breeders routinely screen their new varieties for unintended effects. Recombinant DNA also can produce those kinds of effects.

So there were these concerns, the unintended effects. In some way they're factual, but they can also be hypothetical or theoretical. They're much more difficult to deal with in some respects because you cannot experimentally test every possibility.

Those were some of the kinds of concerns that were being raised, and originally the concerns were, from the environmental perspective, those of transferring genes among organisms in the environment. Could you develop weeds, for example, that would be resistant to the chemical herbicides that were being used, and the weeds then would be able to predominate because they would be resistant? You wouldn't be able to treat them with the chemicals.

SJ: Why would anybody want to do this?

JM: Well, because actually, some of the original, the first food crops that were developed were tolerant to herbicides. Monsanto, for example, had a gene in a common metabolic pathway for tryptophan synthesis that it could make refractory to its herbicide Round-Up and introduce that into food crops so that the food crop could be treated with the herbicide and it would grow fine, but the weeds would . . .

SJ: Okay, I understand.

JM: Right. They had a product that would basically help them sell more herbicide as well as . . .

SJ: That's very clever.

JM: It's very clever, and it was a very simple kind of genetic modification, and so it was very easy to do.

It was one of the first products.

But the first product that FDA was actually asked about happened in the late 1980s, about 1989. FDA began to get questions about food crops. We had been paying attention to food enzymes. Those were cases where the amylase from one organism had been put into another, a better-producing strain to make a better starch-hydrolyzing enzyme for fermentation to produce corn syrup and other food products or . . . The first petition that we had was that we -- I should say the first decision that FDA made on recombinant DNA techniques was for kinesin, which is the more modern name for rennet, which is the enzyme that you normally derive from calf stomach tissues that's used to clot milk to make cheese, and that enzyme was synthesized and introduced into *E. coli*, very similar to the modification that was made to produce insulin.

SJ: Why does *E. coli* make such a good colonizer?

JM: Because there is a strain of *E. coli* called *E. coli K12*, which is a common

laboratory strain known not to be pathogenic and easy to work with genetically. And that's the strain that was used,..Pfizer was the company that made that development and submitted a GRAS petition to FDA for GRAS status for kinesin produced by recombinant DNA techniques using *E. coli*.

I remember that when we first saw the data, it was the purest food enzyme we had ever seen. There really were very few safety questions raised, except they did use a marker gene for antibiotic resistance, and so we did ask them to show . . .

SJ: You put a marker gene in there, a gene that has no real effect, that you know has no effect?

JM: Yes. Well, yes and no.

SJ: What does it do?

JM: To use gene-transfer techniques, you have to have a way to identify the gene, the organism, whether it's a plant or a microbial strain that has taken up the gene. In other words, the successful transfer of the gene, because there is a certain percentage in terms of successful transfers, and to make it easier to find the organism that has successfully received the gene of interest, a marker gene is introduced at the same time. Usually that marker gene codes for resistance to an antibiotic, because that's the way microbiologists have always done developing mutations. It's always been easy to have a -- you can streak something out on a plate, an agar plate, and see if it's affected by an antibiotic. So

it turns out that even with plants, where you're working with germ plasm and growing up these beginnings of a plant, you can put antibiotic in the growth medium because this is not soil at this point, it's more like agar, similar. It's more like a Petri dish. So it turns out that you can use the same kind of technique.

Of course, the question was always, well, if you have a gene that's resistant to antibiotics, is there any possibility that the gene could then somehow become incorporated into microorganisms and provide them protection against the antibiotic, which could have lead to problems in therapy if that's transferred to a pathogenic microorganism? So that was one of the issues that had to be resolved for both the use of these genes in fermentation as well as in plants.

The first product was a tomato. It was a small biotechnology company called Calgene, Inc., from Davis, California, and they had developed a tomato where, instead of introducing a new gene into the tomato, they had isolated a gene that's involved in the ripening, basically the actual rotting of the tomato, and reversed the gene and put it back into the tomato, and that prevented, slowed down, the rotting process.

What it allowed the company to do was to allow the tomato to stay on the vine longer and actually ripen on the vine. The idea was that this would be a tomato that would be a better tomato in the winter in cities like Washington, D.C., where in the 1980s, the tomatoes, if you remember, that we had in the grocery store were often pink and very hard like baseballs and very tasteless. The idea was that if you could ripen the tomato before it was picked and then place it in the grocery store, you would have a better tomato.

And so the only modification was to make a reverse copy of an existing gene in the plant, but they had to use an antibiotic marker gene in order to find the tomato plants in which they had successfully reversed the gene.

What the company wanted to do, of course, was to market this tomato, and they came to FDA realizing that the use of genetic engineering might be difficult for the public to accept, and they wanted to make sure that they had FDA behind them, so to speak.

Well, this was a tomato, and FDA doesn't have any authority for pre-market review and approval of foods. It does for food additives, of course, but whole foods, of course, are introduced into the market, and it is the sponsor of that product's responsibility that the product is safe and is not adulterated, it doesn't violate the Food, Drug and Cosmetic Act, but there's no pre-market review or certification or approval for a food that's placed on the market.

So, for example, when kiwi was first introduced into the U.S., no one had to come to FDA and ask for an approval to place that on the market. That was simply placed on the market on the purveyor's, the company's, responsibility. As long as they're sold as food, there is no pre-market review.

One of the things that FDA realized, CFSAN (Center for Food Safety and Applied Nutrition) realized in the late 1980s was that we had been focused on food ingredients, the things that we normally are involved with in the food industry: food processing enzymes or microorganisms to make vitamins or other kinds of food ingredients, whether they're GRAS or food additives, fermentation products basically.

What the people were really talking about, and in terms of agricultural biotechnology, was huge, potentially huge, because we were now talking about large commodity products like corn and soybeans and cotton. Cotton is used to make oil for food use, so cotton has a food use. But some very major crops now were being modified by recombinant DNA techniques. Then they would be intended for the food supply. So we realized that we needed to make sure that FDA was ready, that these foods would be as safe as other foods. Companies, of course, were coming to us and asking us, how would these foods be regulated, what kind of safety testing would they need to undergo? That was, I believe, one of the first times FDA was really asked the question, how do you apply modern science to show that a food is safe to eat, because most foods are accepted based on the experience we've had or that someone else has had.

SJ: Most food is GRAS.

JM: Yes, we would consider most foods to be GRAS; that's right.

But here we were really being asked that companies wanted to provide that real assurance to the public, and how could they do so scientifically? That was not something that we were prepared to just give them the answers. We didn't have a guidance document that we could just hand them at the time.

In fact, we knew that the conventional ways of testing food additives, single-chemical substances, which are tiered studies with animals, testing studies, toxicology, animal toxicology studies, do not work well or easily for very complex substances such

as whole foods. That's not to say they cannot be done, but we realized we were going to have to think about, what's the best way to approach the safety of these foods?

And there were a number of companies. Calgene was not the only company that came to FDA in the late '80s. Companies like Monsanto had the Round-Up-ready soybean; a company called Ciba-Geigy at the time had a BT (biotech) corn, and there were a few others as well. And basically, in the late 1980s, the companies were approaching FDA, explaining their plans for development for these crops and really asking for guidance from FDA for what they would need to do.

But Calgene actually made a specific request. They were a small biotechnology company. They felt they needed the government's backing, and I'm sure many people in the food industry would tell you they were very naïve to come to FDA and ask FDA for a review of their product, because the strategy they eventually developed was that they decided that the only new substance in their tomato was the enzyme that's produced by the kanamycin-resistance marker gene that they used. The genetic modification to delay and alter the ripening of the tomato, was what was called an antisense, the reverse gene, so it was the gene that was . . .

So they decided they would ask FDA to regulate that enzyme and the gene as a food additive because that would meet the highest standard that FDA has for foods with a reasonable certainty of "no harm". That enzyme was the new substance in the food, and they would show that in all other respects that tomato is a tomato like any other tomato. That was their strategy.

But as it turned out, of course, since we didn't have a set number of tests that they could do, we had to help them work that out between our scientists and their scientists,

and that took time, and it took time for development for the company. The company was learning, FDA was learning. At the same time that we were looking at the specific product and getting information from companies about other products, we were trying to develop a policy of how we would deal with these, because we realized this was going to affect a large part of the food supply, and there were a number of companies doing very similar things. Each had different traits, for example, or different crops they were working on, but there were a lot of common elements to what was being done, and so it seemed important for FDA to be able to provide some uniform guidance to companies to answer their questions. What we wanted to do was answer the questions for the crops that they were developing before they went to market. We didn't want to have to go out and ask the questions afterwards.

When Dr. Kessler became Commissioner, he asked us to develop -- actually, he originally asked us to develop a scientific paper to describe how we would assess the safety of the foods from these new crops. We had already been working on how we would look at the regulatory status and safety and so forth. He really gave us the priority and the mandate to actually focus on it and put the resources into it to get the job done.

Michael Taylor at the time was the Deputy Commissioner for Policy, and he was given the task to oversee the project for Dr. Kessler. I think it was, in my view, the priority that they gave this work that allowed us to put together the group of scientists, lawyers, and other people that we needed to develop the policy, As you know, everyone has so much work to do and priorities, and when you're working with people from many different organizational units, it's very hard to get a large project done in a limited period of time unless it has, it is seen as . . .

SJ: Moved to the top of the queue.

JM: Yes. It has to be seen to be at the top of the queue by the people in the Commissioner's office, and that was the case here.

We eventually convinced the Commissioner that we really needed a *Federal Register* document because we felt that was the best way FDA could put out its thinking to the public broadly and get comments. There was a process there that we felt would serve us well, and we felt this was going to be important enough that we did need public buy-in from all of our stakeholders as we went forward.

What we were asked to do by Dr. Kessler and Mr. Taylor was to assemble a group of scientists from CFSAN. We also included CVM (Center for Veterinary Medicine), which has responsibility for animal feed. Most of these crops are used in animal feed, and so it was a joint project between CFSAN and CVM. And we had Catherine Copp as the counselor from the Office of General Counsel. I'm not sure what they're called today. But the Chief Counsel's office here at FDA had identified Catherine to work with us, and I was the coordinator. All that meant was that I was the person bringing everybody together and collecting all the documents and sending them back out and so forth.

We had a group of scientists with many different kinds of backgrounds, and we spent considerable time looking at the scientific literature. We were given the mandate to look at the science first, set the law aside in the sense of not worrying about whether we had the legal authority to do something if we felt we needed to. What Dr. Kessler wanted

to know first of all is, what does the science tell us in terms of the impact of the use of recombinant DNA on the food supply?

The question was really, in 1986, the government published -- I'm backing up now -- in 1986, the government published a broad policy that was called the Coordinated Framework, and it was one that all the agencies, including FDA, had a section on.

This was written, it was headed by the Office of Science and Technology Policy under the White House, and so it was an interagency effort, and it was written by the Commissioner's office. At the time, Henry Miller and Maryann Danello were the assistants to the Commissioner for biotechnology, and Maryann Danello was actually the contact person in the 1986 Coordinated Framework for the FDA.

The Coordinated Framework set out the various authorities that the different agencies had to oversee products of biotechnology, and the government's broad policy was that there would not be new laws enacted specifically to regulate biotechnology. Rather, the agencies would use their existing authorities . . .

SJ: All of them, not just some of them, right?

JM: All of them, across the government. It did recognize that there may be a need for new guidance, policies, even regulations, but the scientific evidence had shown that there were no unique risks associated with these techniques. It was felt that the existing laws would be adequate to regulate those products, and they were intended to help bring those products into the commercial marketplace, of course.

When, I think part of Dr. Kessler's mandate -- and I should say that in the Coordinated Framework, there was a section where FDA laid out its authority under the Food, Drug and Cosmetic Act for overseeing its adulteration authority for foods, its authority to regulate food additives and the exemption for GRAS substances. That was all described. Our basic authority was set out for regulating food products that were developed through recombinant DNA techniques.

What Dr. Kessler, I think, really was asking us to do was not only to take that a step further, to really look at it more closely. He was really challenging us to ask the question -- the government made this broad policy, that we didn't do anything new, that we could use our existing laws. I mean – was the Food, Drug and Cosmetic Act adequate to regulate these products in the food area?

Well, now, as you know, of course, we faced many new technologies over the 100-year . . .

TAPE 1, SIDE B

JM: So we had a group of scientists, lawyers, and some other folks really looking at the scientific literature, asking what the impact of recombinant-DNA techniques would be on the food supply. And by that I mean we were asking the question of, what kinds of changes were being made in the food crops that would lead to changes in the foods that are produced from those plants? What would be the food-safety questions that one might have about such changes?

What we found was that there were a limited number of traits that were being introduced because there were a limited number of genes that could be transferred, that scientists understood the traits that they could give the plant. So they were basically making plants that were resistant to chemical herbicides; that had changes in the ripening properties such as the Flavr Savr tomato; or they had resistance, which would give the crop resistance to important insects, such as the BT proteins. That is a protein derived from a bacterium called *bacillus thuringiensis*, which is a common insecticide that is used in gardening, for example, or agriculture. The scientists had figured out how to isolate the gene for the toxin from that microorganism and introduce it into food crops to give them their own protection from the caterpillars, for example, that infect corn plants or other common food crops. So they were able, by introducing a single BT gene, to give crops like cotton and corn their own protection from insects.

There were a few other modifications, such as some changes in vegetable-oil fatty-acid content. Most of those came a bit later. But there were essentially a limited number of changes that were being made by the technology in the late 1980s and early '90s. FDA decided at the time that we would try to develop some guidance to answer the industry's questions based on the kinds of modifications that were being made to the food crops at that time, and not try to anticipate where biotechnology would be in 2006, for example.

We looked at the science and asked the questions about what kinds of food-safety issues should be considered, and we felt that because DNA was being transferred from one organism to another, that in itself didn't raise any concern. All of the foods we eat

have DNA in them; all organisms have DNA. So we actually felt they could be assumed to be GRAS.

But the DNA, of course, is being introduced because it encodes information in the cell. It encodes the information to make a protein, in most cases, for example. So the question would be whether the substance that is then produced in the food from that DNA is also safe, whether it's a protein, or in the case of the Flavr Savr, it was the RNA, which is the reverse, the product of the reversal of the gene. But in most cases it's the protein that is the new substance that's potentially in the food.

SJ: Now, was the Flavr Savr tomato successful?

JM: The tomato, the Flavr Savr tomato was a product that the company spent about three, almost four years working on, I believe. We made the final decision in 1994. The tomato was marketed for a very brief time. The company had some other technical problems that were not related to the genetic engineering in terms of growing and marketing fresh tomatoes. And for that reason, the tomato was not successful. It did not become a product commonly known.

SJ: Commercially available.

JM: Right. It was only marketed to a very limited extent and is not on the market today.

But it did provide the FDA with a chance to look at a real product. In other words, we were trying to develop a policy for things that we knew from the literature and what companies were presenting to us, but we actually had a company providing us this scientific data as our scientists helped them design the tests, to review those data. We had an example; we had really a two-pronged example.

SJ: And a fairly simple example.

JM: Right, exactly, a fairly simple example, although the marker gene, raising the issues of antibiotic-resistance transfer, was complicated, whether that gene could be transferred from a plant to pathogenic microorganisms. The food-additive petition itself, actually, was a difficult issue to deal with because it was mostly theoretical. It was not something easily tested experimentally.

So FDA had a two-pronged process. We were trying to develop the broader policy, which became the 1992 policy statement, but we had the specific review of the Flavr Savr tomato and the tomato itself, the scientific information about the tomato as well as the food-additive petition for the marker gene, and those processes were going on at the same time.

So the Flavr Savr tomato really gave FDA practical experience, and the industry as well, and, of course, at the same time, companies like Monsanto were continuing the development of the Round-Up-ready soybean and providing information to FDA as well, and so other companies, on the BT corn and so forth. There were probably about six or

eight companies -- I don't remember exactly -- who were providing some level of information.

But Calgene was unique in that they had actually asked FDA to stand behind them, and we told them we will have to review the data on the tomato in order to be able to . . .

SJ: Support this food-additive petition?

JM: Well, they actually asked for the food-additive petition, but we felt that in order to be able to make some kind of decision -- and when we started, we didn't know what the ultimate decision would be, what the regulatory mechanism would be, except that we weren't going to regulate the tomato as a food additive. We didn't want to ask companies to prove that foods were safe to eat.

In fact, we know that many foods would not meet the reasonable-certainty standard if they were subjected to the kinds of traditional tests because crops have natural substances that would be unsafe if they were at too high of a level and so forth.

Crops have many substances that wouldn't be safe if you actually ask about the safety of that component of the food.

So the company developed the information on the tomato that would show the marker-gene enzyme was not related to any known allergens or toxins; that it was readily digestible like other proteins; its nutrition had not been altered. They accomplished that, they developed data to show that the likelihood of creating a health issue by that marker gene transferring from plants to other organisms was remote, very unlikely. They

showed that the tomato, in terms of its chemical composition, is the same as other commercial tomatoes.

FDA, of course, reviewed all of the scientific information, and before we made the decision, we decided to hold a meeting of the Food Advisory Committee. And we decided that what we would do is we . . .

I should say that we had published our guidance in 1992 in the form of a policy statement, and in that policy statement we laid out the legal framework we had to regulate foods and food additives and GRAS substances and labeling and so forth. The real important part of the '92 policy was the scientific guidance that we put forward, and that included a set of flowcharts where we delineated the kinds of scientific issues that should be addressed in examining the safety of a new food, to find out if it's as safe as other foods on the market. We did that through a series of flowcharts which talked about, what is the source plant? What is it, and what genes are being added to it? And what are the various steps and questions that one needs to go through in terms of, is the new substance in the food a very minor component of the food, or is it a very large concentration of the finished food? Is it related to any known allergens or toxins? There were, as I said, a series of flowcharts to help the industry think through these processes. We didn't define the exact tests that they should do. We felt it was better to allow companies to develop the best tests that they could, and to give them the flexibility to do so, but to make sure they understood what questions should be addressed. And that was the real essence of the 1992 policy. As I said earlier, that was designed to answer the questions about the kinds of food crops that were being developed at the time for both feed use and human food use.

As it's turned out, that policy is still basically FDA's policy today. While some of the science has gotten more detailed, one can do analyses that were not available in the early '90s now, particularly in molecular biology. The fundamentals of the '92 policy really have not changed. The technology has not changed in any way that FDA would need to alter the basic principles it set forth in the 1992 policy.

Getting back to the final decision on the Flavr Savr tomato, FDA decided, before the decision was made, to discuss these issues with the Food Advisory Committee, and we invited not only the standing Food Advisory Committee, but we invited a number of outside experts for that meeting who were experts in gene transfer. They considered the question of whether the marker gene could move from the tomato plant to other organisms, for example. We included experts in various aspects related to plant biotechnology, gene transfer, and other specific scientific disciplines that we didn't have in particular on the committee. Our scientists spent, I think, two full days presenting all of the data that the company had developed to the committee, and we presented our 1992 policy.

Basically, the meeting was structured to show the committee what FDA had set out in guidance and to ask the committee, and to use the Flavr Savr tomato data as an example of one application of that policy as a way of asking the Committee, does this make sense from a scientific perspective in terms of public health protection? The Committee decided, in fact, that the policy did make sense. They felt that the approach made sense and the information about the Flavr Savr tomato did answer the questions that were set out, and so they felt there were no public health issues related with the tomato.

One of the things that was interesting is one of the consumer representatives on the Committee made a comment at one point that, as this was nearing the finish of the meeting, that it was very useful for the company to develop all of this data and for FDA to have spent three-plus years reviewing that data, but it was clearly a large use of resources to review something that in fact, in the end, did not . . .

SJ: Was perfectly safe.

JM: Was perfectly safe. That's right.

The question was, what is FDA going to do about . . . You know, clearly, people knew -- and I think we had even presented the fact that there were other products coming down the pike, right behind, basically; they weren't far behind. And so the question was, what is FDA going to do? Is it going to do the same kind of a full, comprehensive scientific review of all of the products? It might not be the best use of resources in terms of the other things that FDA needs to do in terms of protecting public health, such as food-borne infections and those kinds of issues, or bioterrorism. There are many other things that you need to take all of these things into account in terms of applying the resources most effectively.

What was suggested was that maybe FDA ought to have a more simplified way to look at these products that really don't raise public health issues. That was the genesis of what we call the consultation procedures that are in place today.

The meeting on the Flavr Savr tomato was held in the spring of 1994, and we went back to the Committee in November of the same year, 1994, and that was a joint

meeting with the Center for Veterinary Medicine's Advisory Committee as well. We showed them an additional seven products, including the Round-Up-ready soybean and the BT corn and some other, another ripening tomato, and I think there was the virus-resistant squash as well; basically showed the committee what we felt would be an adequate review where what we had asked the company to provide to us was not all of the raw data, but, rather, to provide enough information so that our scientists could see what issues were addressed, a summary of the data, enough of the data so that we could understand that the decisions that they had reached, the conclusions that they had reached fit with the data, and that the data supported their claims. So while we've often called this a summary of information, it turns out to be more like maybe 50 pages or a hundred pages, sometimes more, so it's not just a postcard to FDA that we have a new product. But, nevertheless, it still doesn't take the kind of intensive review that we did with the Flavr Savr tomato. The committee felt that this was an adequate level of involvement for FDA.

Now, that was always, of course, even in the context that if a product raises questions that are more difficult, more challenging, that FDA would take appropriate steps, depending on the situation. It was also recognized, when we published the 1992 policy, that as the technology evolved, we might need to modify the policy to keep up with advances in the technology. As I said, that hasn't been the case.

Just to finish on the November meeting, our committee had found that the information on the additional seven products was carried out, was developed in a way that was consistent with the guidance FDA had produced, and there were no safety issues with any of those products.

FDA issued letters to companies for those products that basically said the company had made these determinations, and FDA had no further questions. It was the company's continuing responsibility to make sure the product complied with the Food, Drug and Cosmetic Act. In other words, FDA didn't conclude that the products under the consultation were safe and didn't approve the products, but what it did do is, it looked at the data to be sure there was no reason FDA would have to take some enforcement action. In other words, there was no red flag that would say there's an allergen here, that there's not labeling to alert the consumer; or there's a protein here that we're not sure is safe for people to consume; or that the food could possibly be adulterated. There's nothing that indicates that we would have to take any action. This was the kind of process we set up, rather than a full food-additive review type, and approval kind of process. So today, FDA can confidently say it's confident the foods on the market that have been through FDA's review process are as safe as other foods in the grocery store, and that is the standard FDA uses for these foods, that they are as safe as other foods.

In the case of the Flavr Savr tomato, we did reach that conclusion, that this tomato was as safe as other commercial tomatoes, but we also did regulate the enzyme for the kanamycin resistance as a food additive, and there is a food-additive regulation for that substance. So that is the only existing food-additive regulation today, at least so far.

But part of the '92 policy, in terms of the legal framework, explained that foods are really the responsibility of the industry. The act places the legal responsibility on the industry to market safe and wholesome foods, properly labeled foods. But the Act, of course, also gives FDA the enforcement authority to take action if the food marketed doesn't comply with the Act. And so that's basically the way the food system works in

the U.S. The reason companies come to FDA to ask us questions is because they want to make sure that FDA won't ask a question after they're out on the market.

Again, another unique aspect to the law in the U.S. that's different from countries around the world, I think, is the fact we have this balance between the industry having the responsibility for marketing foods and FDA having strong enforcement authority to back it up, so while the industry has the responsibility, FDA does have the power to take action if there's something that can harm the consumer.

At the same time also, of course, FDA has authority to regulate food additives, and a food additive must be reviewed and approved by FDA before it can legally be used in food. There is the exemption for GRAS food ingredients of substances that are generally recognized as safe either based on history of use before 1958 or, in most cases today, based on scientific information that is widely available and recognized by experts knowledgeable about food safety.

SJ: The enzyme in the tomato did not qualify for that?

JM: The company actually asked -- we didn't ask that question, because the company actually asked FDA to regulate that enzyme as a food additive, so they actually submitted a food-additive petition.

SJ: Why would that be the strategy as opposed to just asking for it to be ruled GRAS?

JM: The strategy was that the company wanted to make sure that their tomato had met the highest standard it could meet.

The highest standard FDA has is, for food additives, where they're demonstrated to have a reasonable certainty of no harm. That is a very stringent standard to meet. And because the marker gene -- if it were just a simple enzymatic protein, I think they would have gone the GRAS route, and FDA would have accepted it. But the marker gene, because it was an antibiotic-resistant marker gene, had the additional issue, question, of the potential transfer of resistance to the antibiotic to pathogenic, disease-causing organisms. I actually believe, because no decision was ever made, FDA would have had a difficult time, and we would have asked for a food-additive petition.

Anyway. I think just because of the need to provide a process to make the decision in a way that would be credible to the public . . .

SJ: I was going to say, it seems to me like the best part of this was that even though all that time and effort on everybody's part was put in early up front, it's really been the basis to be able to say, unequivocably, the American public has just not had the kind of scares that Europeans have gone through. I know there are people who still want them labeled and that kind of thing, but we've just never entertained that kind of scare tactics.

JM: Well, there was a lot of interest focused on this in the early 1990s, but once FDA made the decision and went through the public meetings and so forth, most people then, I think, you know, the number of inquiries, certainly, that we got about this really dropped

off. Clearly, there have been interest groups who have been uncomfortable with this technology for different reasons and continue to be, some of them, even today. But even many of the groups who were environmental groups really came to realize that there were clearly reasons why you should look at food safety, allergenicity in particular, and FDA would agree that it's an important issue. But I think they eventually realized that wasn't the primary issue with most of the kinds of modifications.

I also have always felt we had it a little bit easy in the U.S. in the sense that our first public decision was about a tomato. It wasn't about soybean or corn, commodity products that are highly processed and go into many foods where there are ingredients in the foods that consumers aren't aware of or often don't understand.

SJ: It's a tomato that we all knew, in the supermarket, needed improvement, and everybody agreed would have been a fabulous advancement to the food supply.

JM: Right. But people at least, even though the tomato was not widely marketed afterwards, and even leading up to it, people can understand a tomato. They can see it. And there were some of these tomatoes around for a while.

SJ: They could agree on the need to improve them in that area.

JM: And, in fact, it had a modification that was designed to be a benefit to the consumer, unlike all the other products that have come after it, which are really designed for the growers.

That has been something that has been difficult for people to understand, even though -- I don't know the exact percentage, but I'd be willing to bet that over 90 percent of plant breeding is done to improve crops for growers in terms of conventional plant breeding.

SJ: But wasn't the Calgene technology something that could . . . Is it something too complicated to be just licensed, say, to other growers or to people who are traditionally growers? Or does it have to be grown under extremely controlled situations or . . .

JM: Well, once the plants are developed, they make seed just like any other crops, and those seeds then, of course, they're controlled by patents, and there are a lot of business considerations by the companies, and there have been a lot of issues with how these plants are distributed and the controls that companies, some companies have on them. There was a plethora of issues.

And there's been the issue of companies which have not allowed growers to use the seed over again the following years and so forth. So there are a number of issues and I think the FDA did take these careful steps in the beginning.

In addition to making the decision in 1992, Dr. Kessler did actually get his wish. He still wanted his science paper. As we were finishing up and getting ready to publish the 1992 policy, he came back and asked us one day about a science paper as, you know, higher-level supervisors often do. They don't forget about their pet ideas. We thought about that, and in *Science* magazine, which, of course, is one of the most widely read journals in the U.S., there is a section called the "Policy Forum," and we developed a

paper that Dr. Kessler was the chief author, and Mr. Taylor and I and Eric Flamm and Linda Kohn were, I think, the co-authors. I know we were also authors and maybe some others were as well .

But basically, we developed a paper that explained our scientific rationale and approach. I remember we published that, oh, maybe a few weeks, or it could have been a month, but very close to the same time that the 1992 policy was released. Of course, when we released the 1992 policy, it was open for comment. I was much more worried, when we published the paper in *Science*, about the reaction we might get from the scientific community, because this was now going out to scientists. We had done our best in terms of researching the literature. But to me, personally, I was much more worried about what comments we might get back from scientists than -- I knew we would get back generally from the public for the '92 policy.

As it turned out, the paper only generated one comment, which dealt with unintended effects, which was something we had addressed in the 1992 policy. And so, as it's turned out, organizations such as the American Society of Microbiology, I think, supported what FDA had put out. In fact, the policy has been largely supported. It was even the subject of a lawsuit about 2000 -- I've forgotten the actual year; we could find out. But an Alliance for Biointegrity and a whole bunch of other people, some with religious concerns, various kinds of things, sued FDA on some broad issues in the policy, everything from our interpretation of the food-additive provisions, labeling, of course, and religious, there was a religious statute I had never heard of cited. So the policy was challenged.

SJ: Do you remember the name of the case?

JM: It was Alliance for Biointegrity, I think. I actually have a copy of it still at home, I think.

But we put together . . . Actually, I want to put in here somewhere, I have to give a credit to Dr. Linda Kahn, who was one of the chief architects on the '92 policy. Linda was a CFSAN scientist at the time, and when we were developing the policy, Linda suggested the flowcharts. Eric and I kind of groaned about it because we weren't so sure that you could really put all of this complicated stuff into flowcharts in a way that wouldn't somehow be confusing or misinterpreted. But Linda was a different kind of person, and she had the organizational skills to think that through, and she started to do it. As she started to do it, we, of course, became much more interested. That's why there are flowcharts, which I've always thought were one of the highlights of the policy, because, as it turns out, they were done in a way that is very helpful, that doesn't, it's not a checklist; it doesn't come off as a checklist, and I think turned out to be one of the highlights of the policy.

In fact, I remember one company early on, in analyzing one of their products, made a full-cover representation of the flowcharts and showed how their product, the data for their product, fit each of the boxes in the flowchart.

SJ: So they made a checklist out of the flowchart.

JM: Yes, well, they sort of did. I think they were doing it for some promotional reasons.

But I think I've always felt that Linda should get full credit for the fact that we have flowcharts in there.

Of course, all of us, Eric especially, put a lot of effort into making the final version of the flowcharts. But it was Linda who really got us going and convinced us that we could do that.

Linda also helped me with a lot of organizational things and we spent a lot of time on it. CFSAN was divided. They had the Vermont Avenue office where they had the food-additives group.

SJ: Alan Rulis?

JM: Alan Rulis's group, right, and Linda was part of that group, and I was working for Bob Lake in FB-8. Linda would come to my office. We were doing a lot of work together and she was spending a lot of time there. We got a Congressional request for basically everything about biotechnology at one point.

It turned out we sent the congressman 40,000 pages. We basically sent him everything that we could find, including my desk agenda, you know, my desk calendar, and some wall scribblings that Mr. Ronk and I and others had put together when we were thinking through the early stages. We put together all this stuff, and Linda organized it.

She had all these files in my office, and she had it nicely organized so that we could send it up to the Hill.

We grumbled a lot about having to do that at the time. But when the lawsuit came up, we had a record. We had our administrative record almost all put together.

And I remember Anna Marie Kempic was the lawyer from GC who was assigned to the case. She and one of her colleagues from Justice came down one day to see the file in the early part of getting started on the case. I knew that as part of that record, we had all sorts of stuff in there, as I said to you, that included every draft of the '92 policy, and we had all the memos that various folks had written. And in some of those memos in the early part of developing the policy, people were critical and said they didn't like this. They didn't think we should be doing this. They thought this wasn't consistent with the science, and they raised concerns about it. Linda was one, and a couple other people had written those. I knew those memos were in there and could be used. You know, they would not give the best impression. So I made sure to show those to Anna Marie and other lawyers that came down to look at it. And they said, "Oh, that's good. That's good because that shows that you had taken different opinions into account." And I said, "Yes, we did, and at the end, everybody was comfortable with what we came out with."

But what was interesting is, one of the lawyers who had sued FDA went around the world, and still today you see this issue often on the Internet, that FDA scientists disagreed with the agency's policy. And that's, I told you I did an interview just recently, and that was the issue that had Linda Kahn's memo and that just kept going back to this. I just said, "Yes, that's right."

And we did have very vigorous discussions, and all these questions were thought about and taken into account in terms of the final policy development. I mean, the truth of the matter is, I think we would have been in a much more vulnerable position if we had gotten together a group of people who all thought the same thing, and the court agreed. The court actually made a specific comment about that. But, of course, those out there just ignore what the court said. But FDA won the court case on all counts, and so the policy has survived a court challenge and it survived advances in the technology. Yes, in molecular biology we can look at the genes even more closely today than we could in 1992, but the fundamentals of the policy haven't changed.

TAPE 2, SIDE A

JM: So, to explain how FDA used its food-additive authority in the '92 policy, of course, FDA has authority to regulate food additives, and food additives must be approved by FDA before they can be used in food. A substance is a food additive essentially if it's added to food or if it can become a component of food. There is, of course, the GRAS exemption for substances that I think I've already explained that are generally recognized as safe.

FDA decided that, because Congress gave it that authority to regulate substances that were new in food, that if a protein was a component of a food, such as tomato or corn, by virtue of a gene having been introduced and that was now a new substance in the food, that that really met Congress's intent, unless that substance was GRAS, to be regulated as a food additive. So in the '92 policy, FDA explained that if you introduced a

gene into a plant, FDA would assume that the gene, the DNA, is GRAS because that's the same chemical in all foods and been consumed, obviously, for centuries.

But the protein could be different; proteins can be different, and not all proteins are safe, but most proteins that you would expect to find in the food supply, of course, are safe. But what FDA said was that if the new substance that's the result of the expression of the DNA that is in the food is the same protein that's already found and been safely consumed in a food crop -- in other words, if you put a gene from corn back into corn or into some other food, it's producing the same protein -- then FDA would presume that it was GRAS. It wouldn't use its resources to go through the effort to actually affirm or decide that it was GRAS, but it would be reasonable to conclude that that protein had been safely consumed.

We also went a step further and said that, because there are many genes that produce proteins that have slight variation, that if a protein is very similar to proteins that are consumed in food, we didn't believe that small changes in the structure of a protein would change its safety in terms of being consumed as a food substance, in most cases. Now, there are some exceptions. But generally, if a protein, for example, in the case of the Round-Up-ready soybean, the gene is actually found in other organisms such as bacteria, but it's essentially the same enzyme. Many organisms have the same metabolic function, so you find the same enzymes, even that we as people have in our systems, in plants, in microorganisms, and so where the gene is essentially the same, FDA would presume that that also was GRAS.

However, if a gene, or if a protein -- excuse me -- is very different from the proteins that are commonly consumed, or there's some reason that one cannot presume that that protein would be GRAS, then it should be regulated as a food additive.

As I've explained, Calgene actually asked us to regulate the kanamycin-resistant protein as a food additive, so that is an example of a protein regulated as a food additive.

Up to now, most of the genetic modifications of crops developed by recombinant-DNA techniques have involved genes that encode enzymes that are common metabolic enzymes, and they produce proteins that are very similar to proteins that are already found in foods. So FDA has not, to date, asked for food-additive petitions for any of the proteins other than the one that Calgene actually requested. That's a function of the technology up to now. There could be some proteins in the future that FDA would determine needed to be regulated as food additives. But generally, most proteins would not raise the kinds of questions that . . .

I think the important point is FDA has this legal tool to make sure that if something is introduced into food whose safety is uncertain, FDA can use the food-additive authority to make sure that this additive is reviewed and shown to be safe before it's permitted in the food. At the same time, we have the great flexibility that GRAS provides industry and FDA in that the agency doesn't have to ask for specific review of all of the proteins which really don't raise any questions. So part of the consultation process is looking at the new proteins to be sure the company's decision that the protein can reasonably be presumed to be GRAS is a good decision. Really, I think the most important part of the consultation process is in making sure there isn't a food additive involved in that particular product which would require pre-market review by FDA

before the food is introduced to the consumer. So we have a lot of flexibility in our policy.

SJ: Once again, the 1938 Act and the 1958 and ’60 amendments proved to be able to survive the test of time.

JM: As they’ve done with other technologies that FDA has seen.

As it turned out, the 1986 policy was sufficient that we didn’t need a new law, but we took a very careful look at that, and this was the genesis of the 1992 policy and the paper in *Science* and so forth.

Today, FDA has received submissions for over 60 varieties of food crops, everything from papaya, soybeans, corn, cotton for cottonseed oil, canola, tomatoes, squash, and for various modifications, mostly for traits for the grower, and has reviewed those submissions. There is a website where the submissions are listed and you can actually go and look at FDA’s memo summarizing its evaluation as well as the letter that it provided to the company.

So even though this is a voluntary system in the sense the consultation is not required, it’s not legally mandated that companies come to FDA. FDA has given the message to the industry that the agency believes this is prudent practice. We said in the ’92 policy, that we felt it’s prudent for companies to discuss products and new technologies with the agency, and so FDA has made a very strong case these companies should come to FDA with their new varieties of recombinant DNA derived crops. And that has been the case. Companies, of course, have found this a very useful process. To

date, as far as we know, all of the products that have been released as commercial products into the U.S. market, at least intentionally, by the companies have completed the FDA consultation process before they are introduced. The system seems to work very well.

I think many outside don't really understand it because it's a voluntary system. But I always remind people the Food, Drug and Cosmetic Act is not voluntary, that the requirements of the Act and the legal duty the Act places on the developer is a mandatory one, that they are obligated to market foods that are safe and wholesome, or if they're adulterated, obviously, FDA has the authority to take action. It's a voluntary process that works.

Most countries around the world have regulated this technology and have introduced pre-market approval systems that are more the full kinds of review and approval systems.

SJ: In this case, our historic experience with this has made us more comfortable in some respects.

JM: Yes, it has. Our experience . . .

SJ: We have a more fully developed regulatory system that, instead of being constricting in this respect, is actually a little less bureaucratic?

JM: We had a legal framework in place that had enough tools in it that we could

accommodate this technology in a way that FDA felt, and others from outside of FDA clearly have felt, provides adequate public health protection.

I mean, actually, in terms of public health issues, this is very low on the totem pole of potential hazards for the public.

It's very important in terms of public credibility and public understanding that the government in fact does have in place a program that . . .

SJ: And does take this seriously.

JM: . . . takes it seriously, and that these foods don't just wander into the marketplace.

The foods developed by this technology undergo far more testing than all the other foods that enter the grocery store, for food safety. There's really a huge burden that's placed on the developers to use this technology, and that is going to be an issue for developing countries and an issue for small companies. It is, in fact, scientifically difficult to justify a lot of the testing that is being done today for these foods in terms of the public health issues that they actually don't raise. But most of this is now being done to provide confidence to the public that the foods are safe. And even though this technology has now been reviewed in terms of food safety assessments, and we have over a decade of experience, but it's still new. There are still people who have never heard of it; there are still countries who are trying to put systems in place to deal with these products.

The U.S. and Canada, North America, of course, are primarily producer countries. Other countries around the world are still primarily importing countries.

So the whole international picture has become quite complicated as a result of the introduction of this technology, particularly because many of the products are commodity products, large commodity products, such as corn and soybeans, and those products have always moved in commerce based on the quality of the products and what the buyers demand.

But once countries began to put approval processes into place -- for example, Japan has a pre-market approval for biotech crops, and so does Australia and Europe and a number of other countries, Korea, for example; China now has become one of the emerging players. But once those approval products went into place, what it meant was that any variety of corn, for example, that is produced with recombinant DNA techniques must be approved in the receiving country before it's legal.

Corn, as a commodity -- in the U.S., we have many different varieties of corn that are grown and mixed together and sold as one variety, you know, one kind of commercial corn. Primarily this is animal feed. Some corn, of course, is used for food, but most of the corn from modern biotechnology is used for animal feed. Those varieties, maybe through the government system in the U.S. and passed all the regulatory steps they need to do, but they are mixed, then, with conventional varieties of corn. When those products then are shipped to a country such as Japan, if that variety, if that shipment contains a variety of corn that may have been through the system in the U.S. but hasn't been approved in Japan, that shipment of corn is deemed illegal in Japan. There have been any number of cases where that has been . . .

Of course, the industry has had to set up ways to make sure approved varieties, so to speak, are the only ones that are shipped to the various countries. But every country

has its own approval process. And so the whole commodity-trading business has become much more complicated by the fact there are all these different varieties that are approved in some countries but not other countries. From the commercial-trading perspective, it has become very complicated.

SJ: To track all these?

JM: And companies have a problem because they, as I said, maybe have done everything they need to do in the U.S. to market corn domestically, but once the product goes out into the international market and is shipped to many different countries, they have to be sure the varieties are approved in those countries. There have been any number of problems that have come up because varieties have not been approved in the receiving countries.

So those are not problems that directly fall under FDA; those are trade issues. But the FDA is, of course, affected because it has the responsibility to oversee these products in the U.S. so it has become quite a significant problem internationally.

Internationally, food safety has reached a level where there is now a common understanding. From early on, we, of course, were not only looking at these issues within FDA and among ourselves, but with other governments as well, other health agencies around the world, particularly in the U.K. and, of course, Canada, Australia, some other countries in Europe, and Japan. We have worked very closely for years with Japan.

In 1999, the Codex Alimentaries Commission, which is the body under the WHO, World Health Organization, and the FAO, or the Food and Agriculture Organization of

the U.N. -- those are the parent bodies of what is called the Codex -- decided that the Codex should look into developing some international standards or guidelines for biotechnology, since clearly food is a global business, essentially, and the Codex has the responsibility for establishing international standards and codes of practices for foods both to establish standards for safety as well as to ensure fair practices in trade. So the Codex established a temporary committee. It has a big, long name, called the Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology, but we tend to call it the Task Force, or the Task Force on Biotechnology.

The Task Force was set up in 1999 and given the mandate to develop standards or codes of practice or guidelines for food safety for foods developed by modern biotechnology. Japan was asked to chair the Task Force, and they were the chair of the Task Force. Over the four-year period that the Task Force met, it developed guidelines for foods derived from crops and foods derived from microorganisms, foods, for example, to produce yogurt or other fermented foods.

The Task Force was highly successful. In fact, Codex, as an organization, has a reputation for moving rather slowly, but this work actually progressed in record time for Codex in producing two sets of guidelines as well as a set of general principles for looking at the safety of foods from biotechnology.

SJ: In part because we had already put our successful policy into practice, or in part because other groups have done the same thing?

JM: In part because we and other countries like Canada and Australia by that time had

considerable experience in reviewing these products, and we had all essentially reached the same kind of approach, that approach that was set out for looking at these foods scientifically was really agreed to. There were a lot of common elements, in other words, to what was being done in Canada and the U.S. and Australia and the countries in Europe who actually had experience in doing this, and Japan. Those countries in particular had considerable experience.

We had discussed some of these issues as well through the Organization for Economic Co-operation and Development (OCED), so some general documents had been put out through OECD. There were some early expert consultations by Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO). Sandy Miller, who was the director of the Center for Food Safety and Applied Nutrition (CFSAN), chaired the first FAO/WHO consultation on biotechnology in 1990. So there were several expert FAO/WHO consultations.

The Task Force was established in 1999 to really take a concerted look and put together some international guidelines, and which were extremely successful. I think everyone has recognized Japan did a really admirable job of both organizing and carrying out the work of the Task Force, providing the basis to do it, and they provided a chairman, Dr. Yushakura, who was an extremely capable scientist. He had no knowledge about food safety -- he's a virologist but very capable -- and is still the chairman today of that committee, but was highly respected by all the delegations.

The Task Force consisted not only of governments from around the world, but also industry and public-interest-group representatives. For example, Consumers International was a very active player, and Dr. Yushakura, in his role as chair, really

made sure that all of the delegates played essentially an equal role. Their ideas were all taken into account.

What was really impressive was at the end of the last meeting, when it came down to agreeing to these guidelines, it was unanimous.

Consumers International, the industry, the government, countries' representatives -- even though we had had a lot of difficult discussions, there was a real consensus about it.

Now, granted, if you look at the document, you could see it can be interpreted a little bit differently depending on how you may want to interpret the issues, and so it's a good Codex document, in other words.

But I think the important thing is it really did set out the framework which people could agree to generally. While there may be differences in the exact tests that one government will want to do versus another, that's just part of science. Scientists never fully agree on anything, actually. But there is today an international approach that's agreed to and recognized, and while there will be modifications in the future, of course, I suspect it will be fundamentally sound for some time to come.

The Task Force has continued. As I said, it was temporary for four years. It has been reactivated this past year and has taken on work to develop guidelines for transgenic animals, things like the fish, for example, that gets in the news a lot.

There are fish that are modified to grow to adult size faster with the growth hormone. These are fish like tilapia and salmon and so forth, common fish that have been given extra copies of the growth-hormone gene so they can reach adult size basically faster, more economically. So the Codex is now developing guidelines for, not

only fish, but other transgenic animals as well, and guidelines for food crops that are modified to have special nutritional properties. That's something that's seen as a future wave of products.

SJ: Well, that was on my list to discuss as well. It's not so critical in the United States, but it certainly was probably one of them, if we talk about the tomato being a popular product in the United States and everyone acknowledged could use some improvement, especially in the winter months. Golden rice, I suppose, was the one that got our attention internationally, the possibility of actually preventing disease on a widespread basis from just the genetically modified commodity.

JM: That's right. Golden rice, of course, is a variety of rice that's modified to produce beta-carotene, and beta-carotene is a precursor for vitamin A. In a number of developing countries, people have a deficiency of vitamin A, and, of course, obviously, there are mechanisms and possibilities of supplementing the diet with vitamin A. But it doesn't work; so far, at least, hasn't worked well. So the idea was, if you could provide a staple food with a source of vitamin A, that you might be able to reduce the incidence of night blindness, for example.

Golden rice is still under development. It has been the first variety that was developed, has been improved. As far as I know, it's undergoing some examinations to see if it, in fact, nutritionally will work. But it's an example of modifying a food in a way that has a particular nutritional enhancement that would benefit consumers. As you said,

it's not designed for a country like the U.S. or Europe, where you have a balanced diet generally. But for developing countries, a product like that has potential.

There has been a lot of discussion about other modifications to provide consumers with health benefits in foods through biotechnology. So far, that has been more ideas and -- probably, certainly there's some research. Some hype.

You know, it was certainly learned from consumer surveys that people were not so enamored with new food crops produced with a new technology that were really designed for the grower, not for their own direct benefit. So the idea was, well, maybe if companies could come up with products that would be seen as more directly beneficial to consumers, it would be easier to accept the new technology. But, in fact, the products really have not been directly beneficial to consumers. Developers so far have not come forward with products that really would have those kinds of attributes in a way that they reach the grocery store, much less they haven't even reached FDA review for the most part.

SJ: Well, we heard a lot about vaccines being delivered through food.

JM: Yes.

SJ: Is that related or even covered by . . . That would require a task force, I would guess, between CBER (Center for Biologicals Evaluation and Research) and CFSAN?

JM: Well, I don't know as much about that, but yes. Charles Aronson, who was at Cornell and I think is now out in Arizona, was one of the primary developers of the idea of being able to produce a protein in a food that could act as an antigen to develop an immune response, basically to make the food be a vaccine. He did use a gene for an *E. coli* toxin in potato and was successful in at least developing immune response. But the people had to eat raw potato, and so not a very palatable food.

The idea was really, in developing countries -- again, this was really a product designed for developing countries, where you'd have a great deal of difficulty in getting vaccines to a population because of distribution problems and so forth. Ultimately what he was thinking about was, if you produce a banana that had a vaccine to infant diarrhea, for example, or some other common diseases, that you might be able to provide a ready source of that.

There was an interesting article just recently in *Science* where he discusses this, and I guess the technology is still a long ways from fruition -- he still has some hopes for it, but there are a lot of economic reasons why it's difficult, and so far it still is on the drawing board.

SJ: Highly experimental.

JM: Highly experimental, but an interesting idea.

Of course, you know, what I remember is from the pharmaceutical, drug side of FDA. This is a great idea. It's potentially easy to purify a protein that could be a drug vaccine kind of product from something like corn, because corn is chemically fairly

simple. On the food side, they say, "Well, that sounds like an interesting idea, but how are you going to make sure that corn doesn't become part of corn flakes?" In other words, even if it doesn't pose a public health hazard, people aren't going to like the idea of finding that their corn flakes have a drug in it.

SJ: Somebody mixed it up or somebody didn't . . .

JM: Somebody mixed those varieties up. And you know the StarLink story well.

And so we know that commodity products from the food perspective, is, how can you make sure that a food crop, a crop that's normally used for food such as corn, if it's designed to produce a pharmaceutical, can be kept separate from the food chain? There are some people who believe there are ways to do that.

SJ: Well, you know, we used to require that pesticide-treated wheat be colored pink to be clearly identified. I don't know if it's possible to do that kind of thing today, but . . .

JM: Well, that's one of the things that some people have thought about, is whether you could add a color to identify that.

There was a soybean developed with a protein from Brazil nut, and the idea was an interesting idea again. It was to make -- soybean lacks certain amino acids, and so when used as animal feed, you have to supplement the feed. If you could balance the amino acid, basically make the protein a higher-quality protein in the soy, you would

have a better animal feed. The idea was that the Brazil nut had a protein that had the amino acid which was needed and that could potentially create a more high-quality protein. So a company isolated the gene from Brazil nut and introduced it into soybean, and the plant was grown. They, of course, looked at FDA's guidelines and said, "Well, one of the things we have to determine is whether this protein could be an allergen. A number of people in the U.S. population are allergic to tree nuts, including Brazil nuts.

The protein was actually one of the major proteins of Brazil nut. It's what they call a storage protein. It's when you have a seed, the seed has protein that's there for it to grow into a new plant, and so it's one of the major components of Brazil nut.

Not surprisingly, when they did tests for allergenicity using the skin-prick kind of test on individuals who are sensitive to Brazil nut, they found that these individuals were also sensitive to this protein that had been introduced in soybean. So the product was discontinued as a commercial product. It was never commercialized.

SJ: But it would have been consumed by animals, not humans.

JM: Well, that's right. It was designed as an animal feed. But the question was, how do we make sure that this soybean does not get mixed up with the soybeans used in human food?

And the company -- you mentioned color. Well, one of the things they thought about, was there some way to color these soybeans to distinguish them, and they really couldn't come up with any practical way to make sure that that soybean wouldn't get

mixed up at some point in the process. So the product was discontinued. It never became a commercial product.

But it did show that the food-safety assessment process worked, that if you went through the scientific analysis, you could, in fact, identify this protein that would be problematic. So in a sense we've always been happy that they developed that product because . . .

SJ: It taught you something as well.

JM: It also taught us that allergenicity was not just hypothetical, and I think most people would agree today that allergenicity is the one issue about transferring genes and, therefore, proteins from one source to another that really is the key issue. It's very unlikely a protein would be a toxin if you understand its function and what it does.

Allergenicity is a difficult issue, and in particular if that gene is derived . . . Now, companies know now they don't want to move a gene from a source that's known to be allergenic into another source unless it's very clear that gene is not an allergen.

That is really the key question, I think, about the safety of these foods -- not because it's likely to happen, but it's because it is a real potential for some proteins.

SJ: That leads into the StarLink corn episode and -- actually, I want you to start with that. Now, from the very beginning you're dealing with agricultural commodities. What was the relationship between USDA (U.S. Department of Agriculture) and FDA? Was there either some competition or some camaraderie?

JM: Well, actually, in terms of biotech, I always had the feeling that there was a lot more cooperation among the agencies on biotech than there were in some other areas. It seemed to be, I seemed to hear it. Some things just gave me the sense that we actually had more cooperation. Of course, there was an interagency collaboration in developing the early 1986 policy statement and so forth. Obviously, there are always tensions between agencies. But we had various informal get-togethers from the early days.

FDA, EPA **(Environmental Protection Agency)**, and USDA are the primary players in terms of regulating agricultural biotechnology. In the late 1980s, the three agencies conducted a conference just generally looking at -- and then the primary interest was in the environment. People had to grow the crops before they had foods.

SJ: Where was the conference? Do you remember?

JM: It was held here in Washington, that conference. I've forgotten exactly where we held it, but I just remember that the three agencies sponsored a conference jointly, and there was a food-safety component to it, but that was very early on, before we had any real examples in front of us at the time.

The agencies then also held a conference, in Annapolis, on allergenicity that all three agencies held to get expert scientists together to talk about how to assess potential allergenicity of new proteins, and that was a very fruitful conference for us.

There was a lot of interaction. Agencies used various different mechanisms, but they interacted quite a bit in the early days.

Clearly, there were some clear delineations of authority. USDA, of course, has the authority under the Plant Protection Act to protect agriculture, basically. And USDA set up a set of regulations that meant any rDNA crop had to receive a permit for the early growing stages, and they had both a permit and a notification process and so forth. But basically the early field tests were regulated by USDA APHIS, the Animal and Plant Health Inspection Service. EPA, of course, has the authority to regulate pesticides, and a number of the crops were developed to express the BT protein, which is the protein from *bacillus thuringiensis* that is effective against insects. It basically kills insects, like the corn borer, for example. And so EPA has the oversight over those for both food safety and environmental issues. FDA, of course, has the authority for any modifications that are not pesticides, and for the labeling of foods. So some of these products, such as a BT corn, would fall under all three agencies; the growing for field testing for APHIS; the regulation of the pesticide trait by EPA; and the safety of the food or feed derived from that crop by FDA, and the labeling by FDA. So a crop like BT corn would fall under all three agencies.

An herbicide-tolerant crop similarly would fall under APHIS for the field testing and FDA for the safety of the gene, the protein that's introduced, the herbicide tolerance, because that, while EPA regulates the chemical herbicide, they didn't consider the gene that's resistant to the herbicide to be a pesticide. So that was an FDA product. But EPA, of course, regulates the chemical that's used on that. So, again, all three agencies have some role in product. Primarily in terms of the biotechnology, USDA and FDA are the primary agencies for crops that don't have a pesticide actually incorporated into them.

EPA, I should say, made a similar, sort of an analogous decision about their authority applied to crops, that a pesticide, if a plant produces a substance that's a pesticide, it would be regulated similarly to one containing an added chemical pesticide. They're analogous. The FDA said if you produce a substance, a chemical, and you use it in a food manufacturing process and add it to food, it may be a food additive. If you put the gene in the plant, that you're now producing the same substance that's a food additive over here, it's still a food additive. So they are very similar kinds of approaches, but EPA doesn't have the GRAS exemption. So where there's a pesticide, that is a pre-market approval in a sense. It's a registration and a pre-market review by EPA. So the three agencies had those different authorities, which of course was all spelled out, in general at least, in the '86 coordinated framework. So there was good collaboration.

Later on, when StarLink happened, StarLink was a case of a corn variety that had a BT trait, pesticide trait, and so that corn variety, like other BT traits, fell under the authority of EPA to review the BT trait. And EPA had the information to approve that trait for use in animal food, but there were some characteristics of the protein that were similar to characteristics of allergens. So part of the assessment of potential allergenicity of new proteins is to compare the protein to the characteristics of known allergens, and most food allergens tend to be resistant to digestion, to heat or digestion conditions. The StarLink protein had some of the characteristics. It was not as digestible as other proteins.

It didn't have enough characteristics to basically definitively say that it would be an allergen, but EPA didn't have enough information to decide one way or the other, and

they had several meetings of their advisory committee. That committee recommended that protein be considered to have a moderate . . .

TAPE 2, SIDE B

JM: So EPA was able to reach a safety decision that StarLink could be registered for use as an animal feed or for industrial uses, that that variety of corn, called the StarLink corn, could be used for industrial uses or animal feed, but they could not approve it for use in food.

The company believed they could set up a program whereby they could keep that corn in the industrial-feed chain and keep it out of the food supply. I remember they came to FDA and explained their plan to us, and FDA was quite dubious about whether that plan would work. But it wasn't our decision.

So, the company did go forward based on EPA's approval for use in feed and non-industrial use. Of course, as the story played out, a public-interest group detected the StarLink protein in taco chips, which led to a massive investigation by the U.S. government: EPA, of course, having the primary responsibility for the safety assessment of the StarLink protein under the pesticide registration; FDA, of course, having the compliance responsibility for seeing that this illegal substance stayed out of the human food supply. I should be clear about this: the effect of finding StarLink protein in the food supply meant that it was not registered as a pesticide and therefore was illegal. There was no evidence it was harmful to consumers, but it just simply had not been approved, so it was a case of an illegal pesticide. FDA had the responsibility to make

sure that the batches of corn that contained StarLink protein were found and were removed from and diverted to the feed or industrial supply. Of course, USDA, having the responsibility for agriculture, was a major player also.

There was a concerted effort by the government and the industry to deal with the problem, and I think the reason it would not become a huge public health, a huge public concern issue was that the government did take very effective action. It was very complicated because the StarLink corn was found in many different places.

SJ: What was the company's explanation for how this happened in spite of their best efforts?

JM: Well, their system just simply didn't work. The commodity business, the distribution of seed, the growing of corn, and the distribution once it's grown, and the commingling is just so complicated that they underestimated the efforts required to really keep things where they were. Of course, once they sold seed to companies, they had only limited control.

I don't know all the details of how that worked, but basically the process was a miserable failure in terms of keeping the commodity separate. And what the U.S. government learned as a result was just that you cannot depend on having a registration for non-food uses for something which is commonly in the food chain. So today, the government really does not want to have what came to be called split approval, in other words, approval for feed but not for food.

I know that there are definitely cases of conventional products in the past where they've had specific approvals by CVM that were not approved by CFSAN because they had no food use. It's not new and novel to have separate food and feed approvals; it's just that in this case, there's just no way to separate these crops effectively.

Now, in the future, I wouldn't be surprised if someone doesn't come up with a way to do that if there is a reason and FDA finds it needs to make a decision. But I would think that would be one which will have to be very clearly discussed, not only within FDA, but across the government to make sure everyone is comfortable and that you can in fact have . . .

Today I would say there won't be any decisions. EPA has said they will not make any decisions about agricultural crops that are not jointly for food and feed.

So StarLink was a major, very expensive lesson to the government and to the industry.

SJ: I can't remember who I heard from USDA speak at FDA's annual meeting on StarLink, but he basically admitted that it was realized they pretty much had egg on their face. He was eating humble pie at the time.

JM: Yes. It was a huge problem.

As I said, Bob Lake could tell you much more about it than I want to, to be honest.

SJ: Okay.

You know, we've covered everything I've got on my list. But what have we left out from your perspective?

JM: Well, I think we have covered most of it. We've talked about the international. Today FDA has a,consultation process which is working. It is done jointly for food and feed. I think there still is a lot of discussion around the world.

FDA is still being asked to provide a lot of assistance to the trade agencies, for example, in the U.S. who are dealing with these commodities flowing around the world, and to help develop international standards, and to share the U.S. experience with other countries as a way of trying to make sure that food safety reviews are consistent around the world, and that still is a major challenge. There are many countries still trying to figure out how to deal with this technology.

SJ: Are there other ones as vocal as the European Union?

JM: Well, I think that the EU really is the most difficult, and I think it's been very difficult in the EU for a number of reasons.

First of all, in the very early days, the U.K. had approved essentially the same Flavr Savr tomato, but for use as food paste, tomato paste. It was marketed in the U.K. and labeled that it was genetically, I don't know whether they used modified, probably, and marketed along with the conventional. It turned out the consumers preferred the genetically-engineered variety because the paste was a little thicker, was my understanding. But anyway, the point being that it was not controversial when it was first introduced.

Then they had the problem with BSE (Bovine Spongiform Encephalopathy), the mad-cow disease, and people were not confident in the government, and I think that was a major issue for Europe as well.

The other major issue, I think, was cultural, that Europeans tend to be less enthusiastic about new technologies related to food than Americans. Americans seem to be more receptive to new ways to produce foods. Also, Europe at that time was an importer of American products, and so you had the issues of large American companies wanting to market products of a new technology that at least some in Europe were not confident about. That tie-in with the BSE and other problems -- there was a dioxin problem in Europe -- other food safety problems created a lack of public confidence, and I think that alone, of course, was pushed along by groups like Greenpeace. So today, the Europeans are much more reluctant about this technology, so it's been particularly difficult in Europe. I think it's also true in countries like Japan, which were -- Japan very early on essentially followed the U.S. approach. But once Europe became concerned, Japan, of course, also looks to other Western countries, and they, of course, began to feel some of the consumer pressure. So they developed, then, a pre-market review and labeling requirements and so forth.

At least in Japan, they have a workable system, and products do get through their system, although there's nothing in the grocery store. You won't find any labeled foods yet in the grocery store. Animal-feed products are used in processed foods and so forth. But there are no foods that contain genetically engineered ingredients in the grocery store that have to be labeled.

SJ: Can you talk a little bit about the labeling controversy? I know Mike Taylor was intimately involved in defending FDA's position on the issue . . .

JM: Labeling is the other issue we should talk about because it's my least-favorite issue.

SJ: I think it is for most people in FDA, from what I can understand.

JM: Well, FDA, of course, has authority for labeling of food products under the Food, Drug and Cosmetic Act, and so one of the questions was whether there should be any special labeling for foods developed by biotechnology. If you look at the comments FDA has received over the years, or if you look at consumer studies, if people are simply asked if they would like biotech foods labeled, if they want to know if a food is developed by biotechnology, most people will say "yes." It gets more complicated if you start asking more probing questions about whether they want to pay more or why they want the foods labeled. Then the question becomes much more complicated. But the general sort of gut feeling of people is they'd like to have these foods labeled.

So FDA had to consider, as part of developing the '92 policy, whether there should be special labeling for these foods. And so we looked at the science, looked at the characteristics of the foods, and clearly, the foods that were being developed often had special characteristics. They would be tomatoes that contained the gene for resistance to the herbicide, for example; or cottonseed oil that's derived from the plant that has

resistance to the caterpillar. Those modifications, in terms of the composition of the food or the effect on the natural food itself, though, were trivial. They were very minor. They didn't affect the composition of the food in any way that would affect the consumer. And these were things that had been evaluated and found to be safe.

And FDA's labeling authority, where, for FDA to be able to require a company to put additional information on the food label, really says that FDA has to determine that there's some consequence for the consumer. There has to be some material reason why that food is different from its competitor's product. And FDA could not find any basis to say that the mere use of genetic engineering created a class of products that differed in safety or quality or in any uniform, identifiable way, simply because of the use of the technology. In some cases the foods could be different, and they may require a different name because they're different. But as a class, under the Act, we really didn't have the authority to mandate that companies label the products.

So FDA explained that in the '92 policy, and that was part of the court challenge to the '92 policy as well. The court did uphold FDA's interpretation of that. In fact, of course, if FDA were to require labeling of foods simply because they are genetically engineered, mandatory labeling, then it would have to consider other requests from consumers based on the kinds of things they want to know: what pesticides have been used in growing the food; were the foods produced using migrant workers; or any other number of issues that various consumers may feel are important to them.

SJ: "Dolphin-safe" labeling, therefore, is not mandated, that kind of thing? That's an industry voluntary label?

JM: There is a lot of labeling that is voluntary, and FDA's authority is to determine whether that labeling is truthful and not misleading. So the question then becomes, can foods be labeled in a way that will convey information to the consumer so that it is truthful and doesn't mislead the consumer?

JM: What the labeling people I think would say is that, if FDA finds this information is misleading to the consumers, then we can take enforcement action.

SJ: Okay.

JM: In terms of biotech foods, FDA conducted some . . . Well, originally, FDA put out the statement it would not require labeling, special labeling, just as a class. But if there was a change in the food that, for example, the consumer needed to know how to cook the food differently, or if there was an allergen that was unexpected, the consumer would not expect to find in that food, or if there was some major nutritional change in the food, that information would have to be provided.

For example, there is a product that was developed from soybean where the soybean oil contains a high level of a fatty acid, oleic acid. It's a normal component of soybean, but instead of being 20 percent as it is in normal soybean oil, it's now 80 percent in what's called high-oleic soybean oil. That was developed to really develop a high-temperature frying oil. It's not only a different product compositionally; it actually

has a different function. So that part has to be called by a different name. Well, obviously, the company wants to call it by a different name anyway.

There was a second product that was different enough to require a different name. Calgene actually developed a variety of canola oil which contained a fatty acid from palm oil. It wasn't derived from palm oil; it was derived from an actual tree, but it's the same oil that's found in oils like palm oil, and it's called lauric acid. It's the fatty acid, lauric acid. So it was called lauric canola, this was the name they chose for it. But that product actually had very limited intended food uses, things like confectionary, coffee whiteners, I think, very, very limited. It had some uses, possibly industrial uses, but mainly cosmetic uses. As far as I know, it never became a commercial product. But it was an example where the genetic change that had been made led to a difference in the composition that was substantial, and therefore you have to have a different name for it.

Common or usual name in terms of -- in labeling parlance, you would say it had to have a different common and usual name. You wouldn't simply call it canola. Not that the company would want to call it canola.

So FDA did take a second look at the labeling issue and conducted some focus groups and learned some interesting things from the focus groups. One, they learned that consumers didn't particularly like any of the terms that we had. They didn't like "genetic engineering", they didn't like "genetic modification". "Biotechnology" was okay.

One of the things that FDA found was that what seemed reasonable to present to consumers was that if a company wanted to voluntarily inform the consumer they had used "genetic engineering", they could say that a product had been developed by "genetic engineering" or not. But if it was, what they also found from the focus groups was

consumers would like to know why. So, for example, if it was developed to reduce the use of pesticides, if you could show that there was a legitimate basis for that reason, then it might be reasonable to say that on the label, that "this product was developed by genetic engineering to reduce the use of chemical pesticides" or "to make this product to reduce the saturated fat content of the oil" or something.

So far I don't know of any products that are on the market that have this kind of labeling. Food companies have tended to source products that are not genetically engineered or to simply not label them. So the voluntary labeling has really only been used in the negative sense. You do see products which state that they are not derived from genetically engineered varieties. If you look at soy milk, the Silk soymilk, it says that "this product is not made from soybeans that are genetically engineered." And there are other examples . . .

Some companies wanted to, and probably still do to some extent, claim that their products are GMO-free (Genetically Modified Organism). That's a popular term. Genetically modified organism is the Europeans' favorite term, and focus groups really found when you use that word organism, it suggested to people there's something creepy-crawly in the food. So FDA has always taken a dim view of using the term GMO and GMO-free in terms of food labeling because it's not clear to the consumer that there really are not organisms in the food. And if they say that the food is GMO-free, something like soy, we know, because of the commodity process, that even though the soybeans may not have been genetically engineered soybeans which are used to produce the soymilk, there's a very high likelihood that between pollen flow in the agricultural environment or seed mixing, at least a very small amount will in fact . . . In other words,

with the powerful techniques of molecular biology, PCR, you could detect some DNA from genetically engineered soybean, even in products not thought to be derived from genetic engineering. So FDA has always felt you really can't say that the product is free for that reason.

So the agency has guidance on its website to give industry some indications of what FDA thinks would be reasonable kinds of statements to make so consumers won't be misled. In other words, "this product is derived from soybeans that were not genetically engineered" would be a statement which is a true statement. It doesn't say it contains no genetically engineered material.

SJ: But we don't have any examples of companies that have chosen to make a positive statement about it?

JM: A positive statement, no. I can't think of one because there really aren't products that, at the retail level, have advantages to the consumer.

When Calgene first marketed their tomato, they put out a brochure with -- I'm blanking on the term for a brochure that goes with the food product; what do you call it? -- but anyway, it was a foldout brochure and it was round and the color looked like a tomato, and inside it explained about the tomato, and it did explain it was developed by genetic engineering. I still have one, gave it to Kathleen Jones. Someday it should probably come to the FDA archives.

SW: And the label is the most direct link with the consumer.

JM: Yes. I think the real answer to labeling, of course -- FDA has taken a lot of criticism for its policy to labeling -- but clearly that's been supported by the court. I think the legal answer is clear. FDA simply doesn't have the authority to mandate special labeling generally. The answer, of course, would be for Congress to do that.

If the American public broadly really had as much concern as some surveys would have you believe, that concern would be heard in the Congress, and therefore there would be legislation to provide for that labeling.

Now, over the years, there have been a number of bills introduced into Congress to require labeling. So far, none of them have ever generated enough support to become real serious pieces of legislation. But there have been attempts to have Congress act.

I think the real thing in the U.S. is that, as long as there's no accident, so to speak, in other words, something doesn't go wrong in a biotech food, Americans are comfortable. This is not a high-priority issue for them. And there will not be a call for mandatory labeling through the Congress that would result in legislation.

That, of course, could all change overnight if there were a problem like StarLink. For example, a product that was actually, instead of a compliance issue, if that had actually been a public health issue, people actually were getting sick, then things would change overnight. But,FDA wants to make sure this is not going to happen by the kinds of consultation processes they have in place.

The picture will get a lot more complicated over the years as products begin to come to the United States. Now we receive some biotech products from Canada, for example; canola oil comes from Canada. But primarily, we're an exporting country.

China is developing biotechnology very rapidly, as are other countries in South America. It's inevitable that eventually products of biotechnology will be imported to the U.S. The question then will be whether those products have been evaluated by the same kinds of standards, to the same standards which FDA expects, and that is, of course, an important reason for the Codex process and working with other governments.

SJ: My only other related question is, with the experience with or controversy over labeling irradiated food, did that provide any precedent on how to handle some of this?

JM: Yes, it did, and it was -- I remember I used to always try to . . .

SJ: Lessons can be positive or negative.

JM: How many times in my career did I scratch out the word irradiation in documents because there was always this link made, when people would write documents, between irradiated foods and biotech foods.

SJ: Yes.

JM: We always said, "We don't want to be tangled up with them." But the issues were very similar, of course.

One of the interesting things is that, in the case of irradiated foods, FDA did require labeling. And if you look at the rationale they put forward, it was that the use of

irradiation could change the organoleptic properties of the food and that was therefore material. Well, some biotech, the Calgene tomato could be argued to have changed the organoleptic, you know, the ripening properties. That's not much different.

SJ: Irradiated food would spoil less quickly.

JM: Right. And you're changing the shelf life essentially. They're not much different.

SJ: Well, they don't require it for Parmalat milk. The first irradiated product I was ever aware of was irradiated milk, shelf-stable milk. I don't think it has any explanation of why it's shelf-stable.

JM: Basically, irradiated food labeling was often raised as a reason why FDA could require labeling by those who wanted labeling: If you can require it for that, why can't you require it for biotech foods? I think the agency's decision was the right one.

If you look at all of the countries -- I believe it's still true -- that all of the countries which have mandatory labeling, there are no foods in the grocery store that are labeled. It just, the food companies feel that it is a skull-and-crossbones, and that it also makes them targets for boycotts and the kind of violence, even, that some groups are willing to carry out.

SJ: It limits the marketability?

JM: So it actually limits, and what a lot of industry people say is it limits consumer choice because they don't have both. Well, now, that may be a marketing thing.

Basically, if you look at Japan, Australia, and of course Europe, you really don't find, other than there are some cases where, for example, soybean is used in some ingredients that are present at very low levels in the foods that don't rise to the threshold of labeling. So, in Japan, it's used in animal feed successfully, biotech corn, for example, or soybeans, but the food companies all use non-biotech corn and soybeans for their food products. If that substance is going to be in the food at greater than 5 percent of the food because that's their threshold for labeling.

SJ: Well, that's interesting. They have a quantitative . . .

JM: Well, I think for all food products, they're all sourced because they don't want a consumer group detecting even small amounts. Japan is very sensitive about biotech, just like Europe, except not as vociferous about it.

The other interesting story is the papaya. In terms of success, papaya is one of the huge successes of agricultural biotechnology. Dennis Gonzalez, who is a researcher at Cornell University, developed a virus-resistant variety of papaya by taking a protein from the virus that infects the plant and putting it into the DNA of the papaya plant, and it provided an essential immunity to the virus. Well, it turned out that the Hawaii papaya industry was having a very huge problem with this virus. In fact, it was in danger of

going out of business. This variety essentially saved the industry, and it was one of the early varieties.

It turns out that viruses, papaya's naturally, and many fruits and vegetables are naturally infected with these plant viruses that cause plant disease, but they don't cause human disease. So the food-safety assessment about the papaya was very easy in the sense it turned out that the amount of protein which was added by genetic engineering was much less than the natural viral infection that people consume, and so the EPA didn't have much difficulty coming to a conclusion.

SJ: And when was the papaya . . .

JM: Probably -- I've forgotten the exact date, although I've got Dennis's slides he just sent me at home; I could probably find out, but it was probably about '97, I would guess.

SJ: It came under discussion fairly late?

JM: It was a later one. It wasn't one of those first seven that we did. That was a squash. It was also virus-resistant. The papaya was essentially a similar kind of modification. This is a product that has been reviewed by the government in Japan ever since it was reviewed in the U.S., and it's still not approved in Japan. They keep -- and I think the reason probably has more to do with politics than it does science.

SJ: Public health.

JM: Yes. I think they're just not ready for a whole food, biotech food on the market in Japan yet, and that's true of other countries in Asia.

I think the answer is going to be China. Once China starts marketing commercially biotech foods, assuming they do -- and it's hard to imagine they won't -- I think that'll change the whole landscape.

SJ: They've got a lot of people to feed. They can't be as particular.

JM: And they have a tremendously growing economy in terms, including agricultural economy, and so I think that's going to be the turning point. It's going to change the complexion.

It could come from South America too. Brazil is a huge producing country of biotech crops, as is Argentina.

Anyway, I've talked too long, I'm sure.

SJ: You have not.

Thank you so much for giving us your insights into a fascinating subject in FDA's history.

END OF INTERVIEW