

COMMERCIALIZING AGRICULTURAL BIOTECHNOLOGY

Some time ago I decided that every time I hear Jerry Caulder speak, I would remember and try to use one of his quotations. I think it appropriate

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Calgene, an international agribusiness biotechnology company, is developing new varieties of edible oil crops, alfalfa and tomato seed and seed potato tubers.

to repeat his quote from Will Rogers: "It's not what we don't know that hurts us, it's what we know that ain't true that's gonna kill us in the end"(sic). As we talk about the real risks and rewards in biotechnology, it behooves us to remember those words.

I will address the impediments to industrialization and commercialization of agricultural biotechnology. One of the goals of the meeting was to assess "the reasons why many biotechnology innovations have failed to develop as predicted." Well, I would dispute that view.

Biotechnology innovations have come almost exactly in line with what responsible and knowledgeable people involved in this field since the late 1970s and early 1980s have predicted. For instance in the early 1980s, Martin Apple, president of International Plant Research Institute, was widely quoted—whether accurately or inaccurately—predicting plant biotechnology would generate pork chops on trees. If that is the standard as to our progress, obviously we are not there. On the other hand, Tom Urban, president of Pioneer-Hi Bred, the largest seed company in the world and one of the more knowledgeable individuals in this field, still predicts we will not have genetically engineered plant products on the market and making an impact until the year 2000. In many respects, Tom Urban is as wrong as Martin Apple was as to what is going to happen. We are on the verge of having a whole plethora of products that are going to have material, economic and positive environmental impacts on the agricultural arena.

Let me comment on a few of the specific barriers to commercialization and the standing of a few specific products in the regulatory process. Earlier in this volume (p. III), Bob Nicholas presented the regulatory background. I will comment on where we stand in the process, using examples

from Calgene, my own company, because those are the most familiar ones. To date, the U. S. Department of Agriculture (USDA) has issued over 120 permits to conduct field trials with genetically engineered plants. Calgene was the first company to get such an approval in November, 1987, and has since received over 20 such permits. The average time from the day we file with the USDA until we get those approvals is 105 days. That is very reasonable in the context of any federal bureaucracy, particularly the regulatory ones. Calgene's most recent field trial represents work we are doing in genetically engineered cotton which is in the third year of field trials. Under a single permit, we received approval to conduct 34 trials in 12 different states. All of those trials were planted as of the last Friday in May, despite the highest amount of rain in the southern U.S. since Noah built the ark. Those trials will generate data that will not only answer the questions of the safety of the plants themselves, but that data will be shared with responsible researchers in various university systems and within the Food and Drug Administration (FDA) itself. That data will allow the USDA and other regulatory agencies to make appropriate determinations of risks, if any, in going to full commercialization of those types of plants.

The FDA has taken a lot of criticism, and I feel those criticisms are completely unfounded and inappropriate. In fact, FDA has moved forward with this type of technology assessment. Before FDA can decide what regulations they want to issue, they need to review specific data, understand what is involved and what changes really occur in plants. They have to review information that has been generated and that is happening. Calgene filed a petition for the use of a selectable marker and vector in November 1990, asking FDA to review the safety of 80 percent of the plasmid rather than just a specific target gene, in order to separate the issues. There are lots of different ways to file data with FDA, but Calgene specifically selected the advisory opinion route because it is a public process that invites public comment, and because every single piece of data Calgene submitted to FDA is public. Anyone that wants it can have it, either from Calgene or FDA.

In fact on May 1, 1991, in the *Federal Register*, the FDA published a request for public comment. Calgene entered the 90-day period for comments on the safety of the use of the technology. I encourage all of you that have an abiding interest in this to comment. Comments are exactly what FDA wants, and part of this whole process is getting public input. I hope all of you will avail yourselves of that opportunity—the comment period

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closes on July 30. My strong understanding and belief is that FDA will, on the basis of the focused thinking they have done on this topic now, issue some specific guidelines or points to consider. I do not know what the exact format will be, but I expect a decision from FDA before the end of 1991. I believe you will see FDA making a positive determination on the safety of genetically engineered whole foods in the calendar year 1992—a forecast I am totally prepared to stick with.

Next let me comment on agency collaboration—one of the issues in the public arena where people like to stir up trouble. There is the impression that massive gang warfare is going on between various agencies back in Washington, which is not true (with one notable exception that I will avoid). Certainly, in my mind, the collaboration between FDA and USDA is excellent. For the last five years, numerous meetings have convinced me that FDA has the technical competency through all of their various Centers of Food Safety, Center for Veterinary Medicine and various departments of toxicologists and physiologists, to make the scientific assessments necessary to assure the American people that this technology is not only safe but is beneficial.

Let us focus on the major structural impediments to agricultural biotechnology. First and foremost is the nature of the science. There is not a single plant biotechnology product to date that has been delayed by the regulatory process. Plant products have been delayed by the nature of the science involved, the inherent difficulty and the time required to work with plants. I would not make the same statement with microbes, but I assert that with plants, you are talking about both recalcitrant and slow moving science. For example, if you are going to genetically engineer a tomato, the shortest period of time that you can take is about six weeks. And that just gets you to the plantlet. You must still grow the plant, get the seeds and harvest the seeds to determine whether you have affected the reproductive capacity of the plant. Thus, the science is the principal problem. It takes a long time. You can only do one experiment a year. You transform a plant, grow it up and get the results a year later, which tends to make progress move rather slowly. The inherent nature of the science and the fact that you are dealing with the plants is an impediment. A second impediment is the whole base of knowledge in this field. Previous speakers have talked about it and the small allocations from the federal research budget is yet another impediment. Federal research spending in the plant

sciences or agricultural sciences is miniscule. It does not even make the chart compared to the money that has been historically, and is currently, piled into biomedical research. Jerry Caulder estimated that two percent of the total federal research budget goes into agricultural science as broadly defined. Another measure to consider: historically, the National Institute of Health (NIH) has poured approximately three billion dollars a year into research in the human area. In contrast, over three years ago my good friend Paul Stumpf, who heads the competitive grants program at the USDA, was talking about a \$15 million budget in terms of competitive grants. Now it is \$75 million. That is still a drop in the bucket compared to what is being spent in the development of basic knowledge in other areas. Just to give you an idea of the parameters, I calculated that private industry in the U.S. invests \$350 million a year on plant biotechnology research. That is a substantial figure, although again it is not relative to the base of knowledge that we have and need to know. Calgene spends about \$12 million a year and has invested \$75 million in research in this area in the last ten years. The nature of the science and level of knowledge are major barriers to accelerated progress.

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A third major barrier to commercialization and to making an impact with this technology is finance. It is damn tough to raise money in any agricultural enterprise in the U.S. for several reasons, not the least of which is that there is no major business school that serves as a breeding ground for all the investment bankers and the financial analysts in the U.S. Virtually no business schools has courses with agribusiness in the title, let alone agribusiness in the curriculum. So the financial decision makers in this country are totally ignorant of the underlying economics and opportunities presented by the largest single industry in the country. That is why when you go to a Wall Street banker and say, "I've got a great ag/biotech idea and need money", they just sort of stare out the window and look at the clouds because they do not understand anything about it. It is too difficult for them to take time to learn—they would much rather find a guy who has got a cure for AIDS. Then they would say, "Great, I'll finance it. Don't give me any details. It sounds great. Go for it." There is a huge knowledge gap out there.

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Some finance problems are related to frustrations stemming from a failure to meet expectations. Agricultural biotechnology is highly visible.

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Typically, the kinds of products we are talking about here and that other companies in the industry are talking about have been developed in the bowels of large corporate research groups where they have had a ten year gestation period before seeing the public light. Now what has happened is that the only way companies such as Calgene and other agricultural biotechnology companies could raise money to do research was to go public with the prospects of what they were doing at a very, very early stage. People saw for the very first time how truly difficult and long-term science is. Historically, the development of a drug has never become visible to the public until it is in a phase three clinical or has actually been approved. What the public does not see is the ten years required to move a drug along and get it to clinical trials. Public visibility is a cross that we have to bear, a fact of life which increases the difficulty of financing.

I will make a prediction—that there will be no more agricultural biotechnology start ups in this country in the foreseeable future, because it will be impossible to finance them. There are only about half a dozen successful agricultural biotechnology companies at the present time, and I predict at least half of those will be out of business or be acquired by foreign companies within the next two years. That is a particularly chilling message. While lots of people in the U.S. are running around worrying about the demise of the small family farm (which is a socioeconomic phenomenon that is going to happen irrespective of technology) they fail to realize that nine of the top ten or twelve companies, representing over 90 percent of the agrichemical sales in this country, are owned by foreign corporations. Three of the top five seed companies are owned by foreign corporations. If you are worried about a narrow-minded, inward-looking and self-perpetuating focus of technology, there is no better way to have it happen than to have all of your inputs controlled by mega corporations that do not have their roots in this country. People need to start learning a little bit about financing and fostering innovation—instead of stifling it. Otherwise we face some very chilling prospects.

The next issue is the whole convoluted structural situation in international agriculture—the common agricultural policy in Europe, the Farm Bill here. The structural situation here unequivocally discriminates against innovation. New practices are discriminated against, because of the existing political and financial structure. Canola is a good example. Canola is a new crop in the U.S. there are 40 million acres are grown else-

where in the world, but it is new to the U.S. It is easy to show that canola grown in the winter is the only crop which you can introduce as a diversion crop for crop rotation. It is the only alternative to winter wheat in huge portions of the U.S. Even with the new, non-proven varieties we have, you can show unequivocally that a canola farmer can generate \$30 to \$50 an acre more profit growing canola than he can growing winter wheat. But the Farm Bill gives farmers a \$40 per acre subsidy and takes away any incentive for the farmer to innovate. Farmers say "I don't care, why should I innovate?" This is a very serious structural problem. We are making a little bit of headway; the 1990 Farm Bill provides a little more flexibility and that is helpful. But we still have a long way to go.

The final impediment is public acceptance. I echo Walter Truett Anderson's final point — we must learn from experience. Rather than reflecting on the Nataufians' experience as Walter did, I thought about our experience with fruit flies (*Drosophila*). Last week, in the *Wall Street Journal* there was a front page article on *Drosophila* research being undertaken by William Quinn at Massachusetts Institute of Technology. Quinn is particularly interested in fruit flies because the molecular and genetic structure of the *Drosophila* brain is very similar to the human brain. There are lots of parallels and it has been discovered that the fruit fly has developed a learned response. The lowly fruit fly can learn from experience. However, Dr. Quinn is studying a particular mutant group who cannot do so. I would place many of the adamant opponents of agricultural biotechnology in the category of the abnormal fly that Dr. Quinn is looking at, because they simply seem unable to learn from experience. We have had 15 years of successful research and of research expansion without a single person in the U.S. getting ill from this technology. That is a safety record unmatched by any other industry in the history of the world. Even in the wheelbarrow industry, I am sure a falling wheelbarrow killed someone. People have to put this safety record into perspective. The reason we are doing field trials is to learn. We are generating data that allows us to move forward without worrying that the sky is going to fall on us. I think we all should keep that in mind and move forward aggressively to truly reap the harvest of this great technology.

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