Getting to Yes: How to Achieve Pre-Market Approval

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Thenell & Associates is a regulatory consultancy that provides expert advice and support to companies that make and market genetically engineered plants for food, fiber or fuel. We help clients plan and execute product approval strategies and support their R&D programs from discovery through commercialization. Our clients include start-ups, early and late-stage product developers, mature multi-nationals, and universities. With more than 20 years of practical experience working with US federal and state regulators, we've helped two dozen companies advance their commercialization goals.

We also do some biopesticide and biofertilizer work, and have also done work with genetically engineered microorganisms for industrial purposes. In 2006, together with three colleagues in the United States and Europe, I co-founded the Agricultural BioTech Regulatory Network. The ABTR Network is a group of regulatory professionals serving the agricultural biotechnology industry from product concept through commercialization. It's a network of well qualified regulatory experts who specialize in genetically engineered plants and plant products. Today, we have members and affiliates on four continents serving major ag-biotech markets (Figure 1). Through the ABTR Network, we are able to offer clients global understanding and support typically found only in multi-national companies. We need to be able to offer this perspective because what is cultivated here in the United States doesn't necessarily remain here in the United States.

Specialty Crops: Premarket Approval

It is not uncommon for scientist who have deployed genetically engineered traits in specialty crops to fail to initiate the process of obtaining premarket approval, or—having initiated the process—have failed to complete it. Commonly heard reasons for cessation, from university research directors, include:

- "It's not the objective of our research. We are here to do the proof-of-concept, the discovery, to fulfill the obligations of our grant without the intent to commercialize. We publish papers and then move on to the next grant."
- "We don't know where to start."
- "It's too complicated."
- "It's too expensive."
- "There are intellectual property constraints."
- "We have concerns over product liability and stewardship—potential for lawsuits."
- "Without a commercial partnership, there is no obvious outlet for the discovery."
- "No mechanism exists within my university to commercialize."

Taken together, these are daunting impediments. On the other hand, with good planning, the regulatory issues are not overly complicated. I will describe some of the lessons I've learned from working in ag-biotech regulations since 1990 in hopes that it will de-mystify the product-development process and demonstrate that pre-market approval for genetic traits produced by public-sector researchers is possible. My intention is not to make you an expert, but to convince you to hire the best help you can afford when you need it.

Where We Are and How We Got Here

By some measures, biotechnology has been remarkably successful. Since commercial deployment in 1996, global acreage has increased at double-digit rates for 17 years. It has been claimed that agricultural production has increased by nearly $100 billion in that time. Myriad environmental benefits have accrued from changes in weed and insect control measures, from conservation tillage, from reduced mycotoxins, *etc*.

Data published by the International Service for the Acquisition of Agri-biotech Applications (ISAAA) indicate that 28 countries have approved some 325 unique crop/trait combinations to date (Figure 2). And although specialty products were the very first approvals, the vast majority of today's production is limited to variants of two genetic traits in commodity crops. Specific numbers are hard to come by, but I submit that specialty crops account for less than one-tenth of one percent of the 420 million acres of GM crops produced in the world today.

The power of this technology isn't finding its way to green grocers' shops and produce aisles; the regulatory environment is often cited as one reason for the dichotomy between agronomic and specialty crops. With divergent regulatory requirements around the world, premarket approvals have to be acquired country-by-country. Only certain countries have regulatory systems in place, and only some of these have functional systems. Furthermore,

Figure 1. Agricultural BioTech Regulatory Network.

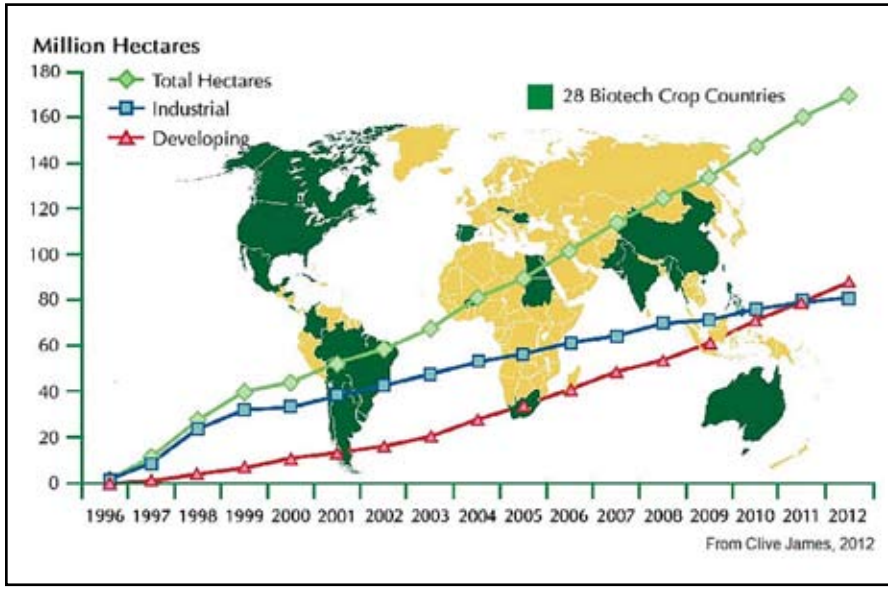

Figure 2. Global GM-crop status.

pre- and post-market requirements vary considerably. Global registration is necessary because, as said before, many of these crops move in international trade. Specialty crops are not necessarily an exception. In the tomato industry, for example, fresh-market produce is the primary outlet, but, additionally, tomatoes go into processing. Similar crops

have components that become ingredients of foods that move in international trade, and issues come up needing regulatory approvals in other countries. Also, only certain countries have functional regulatory systems and certain countries have higher impediments to commercialization than does the United States. Internationally, regulations are not harmonized although there are some reasonably harmonized regulatory risk-assessment criteria. The net effect of this is that when amortized over the thousands of acres of specialty-crop deployment versus the millions of acres in agronomic crops, certain of the regulatory costs make it prohibitive to deploy technology in specialty crops. For this and various other reasons, specialty crops lag behind. I would like to help change that.

Other global instruments have to be considered (Figure 3). The Cartagena Protocol established minimal requirements on trans-boundary movement and use of living modified organisms. It's particularly important in less-developed countries that don't have national legislation governing genetically engineered organisms. Established in 2003, it's based on the precautionary principle, and it has some additional issues concerning advanced informed consent before one initiates trans-boundary movement, as well as liability and redress provisions for environmental contamination that are still being worked out. As of 2013, the Cartagena Protocol has been adopted by 165 countries. But the United States, Australia and Canada are not signatories. Risk-analysis principles—pertaining to genetically engineered food—were promulgated under *Codex Alimentarius* also in 2003; they are internationally recognized as meeting WTO commitments. Those principles are generally consistent with US safety standards and with the Biosafety Protocol. In addition to the WTO agreements, a number of bilateral agreements are in place to facilitate trade including trade in genetically engineered foods and feeds. The WTO agreements have been invoked in trade disputes between members with varying success.

Upcoming negotiations between the United States and Europe will probably include genetically engineered foods.

US Coordinated Framework

In the United States, we operate under the Coordinated Framework for Regulation of Biotechnology Products. Three federal agencies share primary responsibility for assuring safety of genetically engineered plants and plant products, in accordance with their respective legal authorities:

- USDA-APHIS (US Department of Agriculture-Animal and Plant Health Inspection Service)—safety of genetically engineered organisms in agriculture and the natural environment,
- FDA (Food and Drug Administration)—safety of foods from genetically engineered organisms used for food and feed,
- EPA (Environmental Protection Agency)—safety of pesticidal substances produced in genetically engineered plants or microbes.

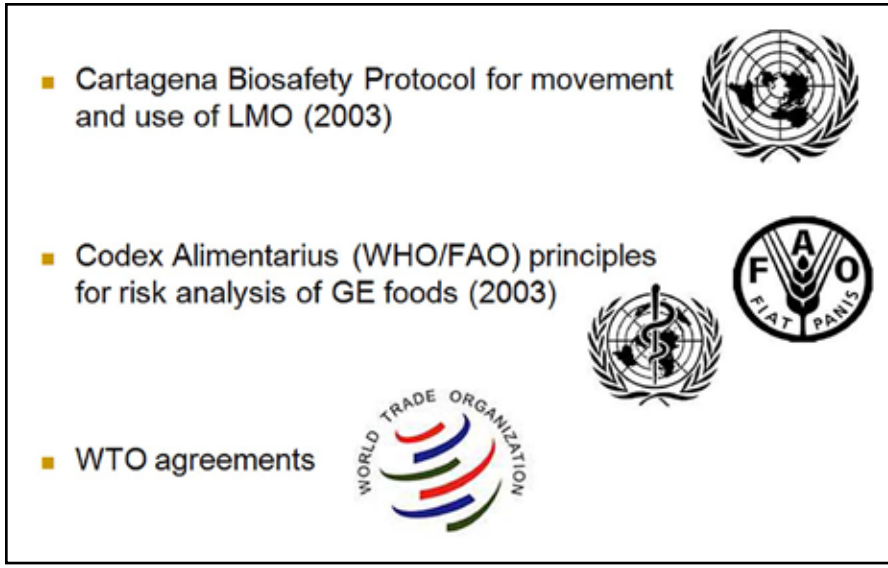

Figure 3. Other global instruments.

USDA-APHIS[1] is the agency likely to be encountered initially when developing and deploying a genetically engineered plant product, in terms of environmental safety, field testing, and/or interstate movement. Bob Merker[2] with FDA mentioned early food-safety assessment for novel proteins that are introduced in field testing so that, should there be any adventitious presence, the food/feed safety concerns would already have been addressed, at least at a preliminary level. And Chris Wozniak[3] with EPA talked about the safety of biopesticides and plant incorporated protectants. This comprehensive—if somewhat complicated—system has worked fairly well since the mid-1980s, although it may be argued that improvements are now needed.

Continuing Controversies

However, even after two decades of commercial use, many recent headlines have focused on controversies around the deployment of genetically engineered plants (Figure 4). Litigations over stewardship lapses and disrupted trade have cost technology providers hundreds of millions of dollars, with lawsuits over intellectual property rights and over government approvals, some of which have made their way to the Supreme Court. As a result, approval times for genetically engineered crops have ballooned from approximately 6 months to over 3 years. Happily, in 2011, USDA implemented process improvements to reduce approval times considerably.

[1]Pages 141–148.
[2]Pages 151–160.
[3]Pages 131–139.

Figure 4. Recent headlines.

Labeling

Controversy continues around labeling. In 2012, Californians failed to approve a labeling initiative at the ballot box, and, more recently, the Senate struck down a labeling amendment in their version of the Farm Bill. Some people remain deeply passionate about the need for labeling of foods with genetically engineered ingredients although no health or safety reason justifies it. The advocacy group, Center for Food Safety, claims that 25 states have introduced bills to require labeling or restrict genetically engineered foods.

All of these issues play some role in the decision to deploy a genetically engineered trait in specialty crops or not.

Product Development

Despite all of the challenges, genetic engineering still holds tremendous potential for improving agricultural yields in the face of continuing challenges from pests and disease, climate change, and population growth. So the question is: *How does one deploy this technology and bring a genetically engineered product to market?* The process involves multiple disciplines working to address various interests that are, oftentimes, not well aligned (Figure 5). The regulatory piece is just one discipline, the purpose of which is to meet all domestic and international approval requirements premarket in those countries wherever one intends to cultivate, to export, or to otherwise market the plant product. The challenge, of course, is to coordinate these efforts to achieve timely completion and enable product introduction to the greatest extent possible. Fulfilling regulatory requirements is often critical to success.

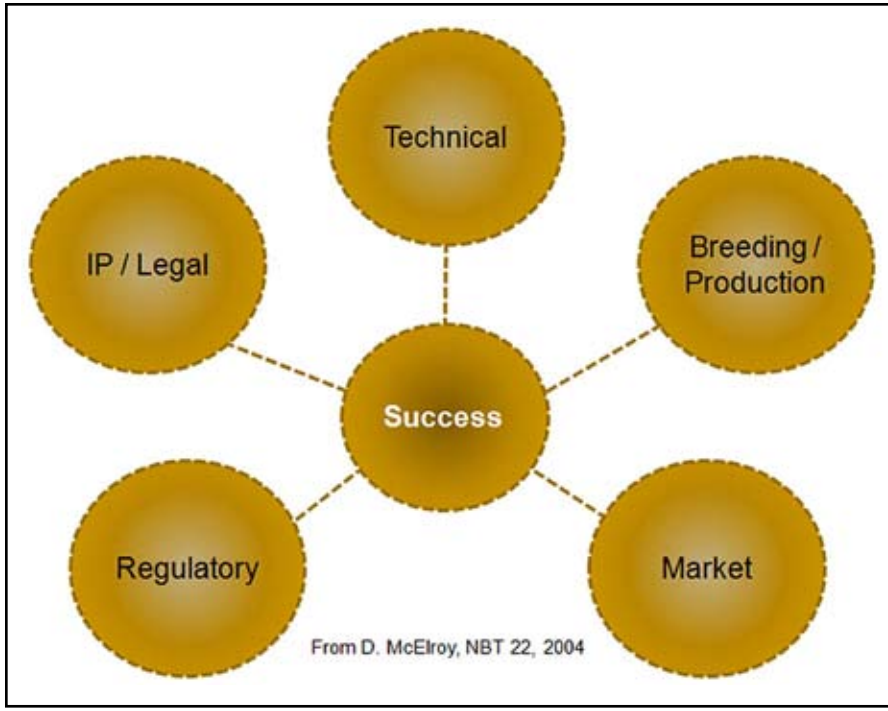

Figure 5. Product development–1.

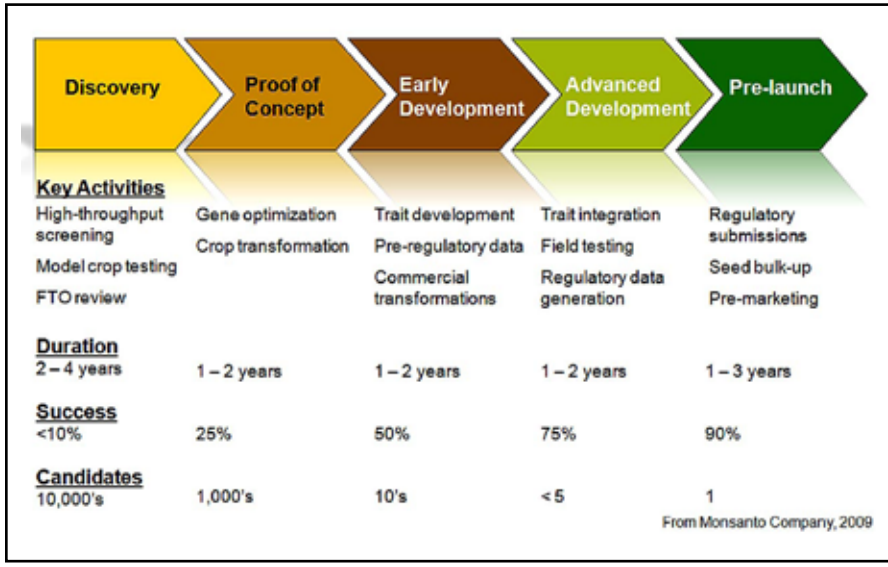

Figure 6. Product development–2.

In the product-development scheme, the major technology providers have adopted some type of systematic approach to creating new crop traits (Figure 6). The process can be organized in stages with defined criteria that must be achieved before advancing to the next stage. By adopting a system of "stages and gateways," the process is more disciplined, thereby helping management of risks and costs at each stage. It can transit from a gene-discovery phase through proof-of-concept, often in a model crop and ultimately in the crop of interest. It moves into an early-development phase in which the trait and its utility are validated, generating pre-regulatory data for the crop intended for market. It advances to trait integration in other germplasm, with field testing to generate regulatory data, and, finally, into prelaunch activities, bulking up seed, and premarketing activities. Duration can vary. Success rate increases in accordance with decisions around event selection, and the number of transformants—the number of candidate lines—decreases until, at the end of the process, focus should be on one, maybe two, commercial events. By adopting this "stages and gateways" approach the process is more disciplined, and it helps manage costs and the risks at each stage.

Regulatory Activities

Each development stage has characteristic regulatory activities and defined criteria for passage to the next stage (Figure 7). The earliest stages involve preliminary analyses of the crop biology and the product concept, and looking at some issues that might occur with deployment of a particular trait in a particular crop species. At proof-of-concept, early work comprises evaluation of whether the active molecule or the technical effect has some human health or safety or environmental safety issue; also analytical tools and reagents are being developed, and protein production and characterization, particularly if additional animal testing is needed, for example. The early stages involve generating protein-safety data on the introduced traits—so-called "core-package" data—and supporting field evaluations and testing. In the later stages, the heavy lifting begins from the regulatory point of view: a number of studies are needed to characterize and create safety data on the lead commercial transformation event—so-called "event package" data—assembling the registration dossiers and managing their submissions. Critically important decisions must be made before entering this phase, as the costs of generating data increase dramatically and the cost of failure at this stage can be high. Molecular characterization is involved as are compositional analyses, agronomic studies, effects on non-target organisms, animal-performance studies, and determinations of environmental fate and toxicology. Finally, at the prelaunch stage, dossiers are compiled and regulatory submissions are managed through to completion.

Much has been said about the high cost of achieving regulatory approval for genetically engineered crop traits. Published numbers range from $6 million to $15 million for global approval. A recent study quoted $35 million for global approval. Although these costs are real, they are inflated inasmuch as they reflect the fully loaded costs of supporting expensive infrastructures to support global deployment. In fact, regulatory approval can be obtained for considerably less—at least in order of magnitude less.

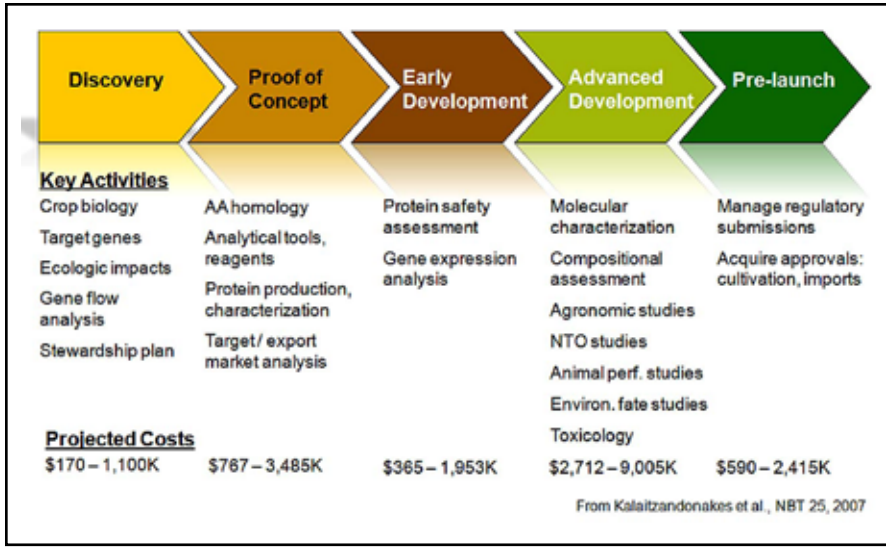

Figure 7. Regulatory activities.

Product Design

Early in their deployment, novelty seemed to drive introductions of genetically engineered foods. However, it soon became clear that market pull trumps technology push. So when asking whether to move forward with the genetically engineered specialty crop, critical questions are:

- Why this?
- Why here?
- Why now?"

The market needs to be assessed efficiently and effectively. It is vitally important to "map" stakeholders to gauge market acceptance and vulnerabilities. Products can achieve technical success, but fail in the market because of lack of acceptance somewhere in the value chain; it can be an expensive lesson.

Regulatory guidance in product design is important (Figure 8). There are myriad places to stumble, but they are largely avoidable *vis-à-vis* regulatory activities. With expert and timely guidance, significant savings are possible in the cost of a regulatory dossier while maximizing the chance of timely approval. On the other hand, I have seen examples of products designed without regulatory input, mainly proof-of-concept projects: "We threw some genes in the plant, we got a great phenotype, so let's make it a commercial product." This can cause significant regulatory heartburn due to poor construct design choices or incomplete information. Seeking out regulatory guidance in the early stages is likely to

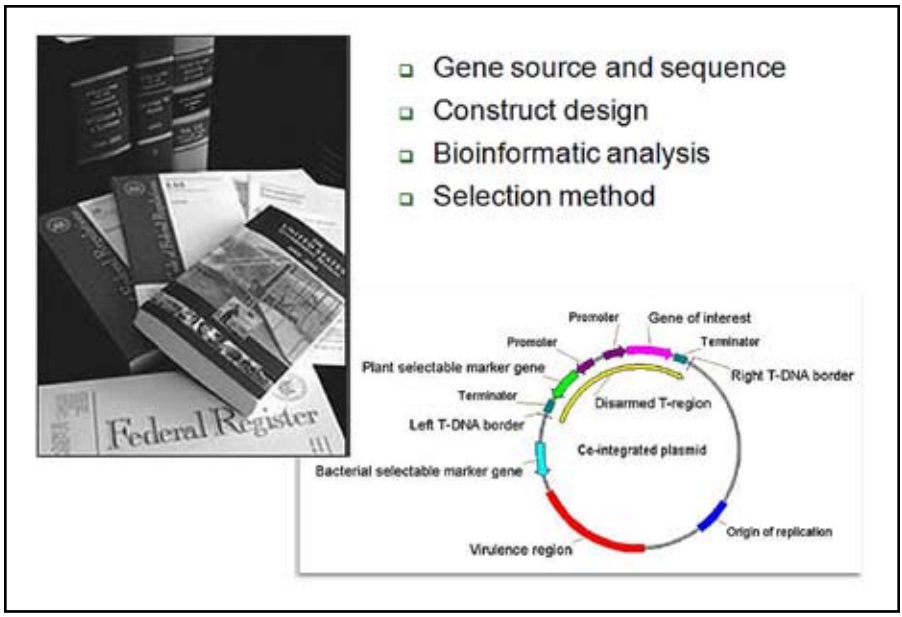

Figure 8. Regulatory guidance in product design.

be a good investment. Strategic and practical regulatory decisions should be considered in product design (Figure 8), including:

- New breeding techniques like precision genome editing can lead to products that are outside the scope of certain regulations and their associated compliance costs.
- For other genetic modifications, early regulatory input on the source of genetic elements, construct design, transformation and selection methods can reduce regulatory data costs later on.
- Conducting a detailed regulatory assessment, at the product-concept or the proof-of-concept phase of product development, is highly recommended.

A good-quality assessment by a consultant will identify the prospective data set, the costs involved, and the timeline to be expected. Once you've "pressure" tested your product design with an expert, it's a good time to consult with your regulatory authorities.

Representatives of USDA-APHIS, FDA and EPA are an excellent resource, and each federal agency has a mechanism by which a developer can meet to discuss their project development. The purpose of such meetings is largely to confirm the regulatory strategy and inform the regulator(s) of the project. It is also an opportunity to confirm the scope of data necessary for pre-market approval before commitment to expensive studies. Depending on how novel is the crop trait or technique is to the particular agency, there should be several consultations during the course of product development (Figure 9).

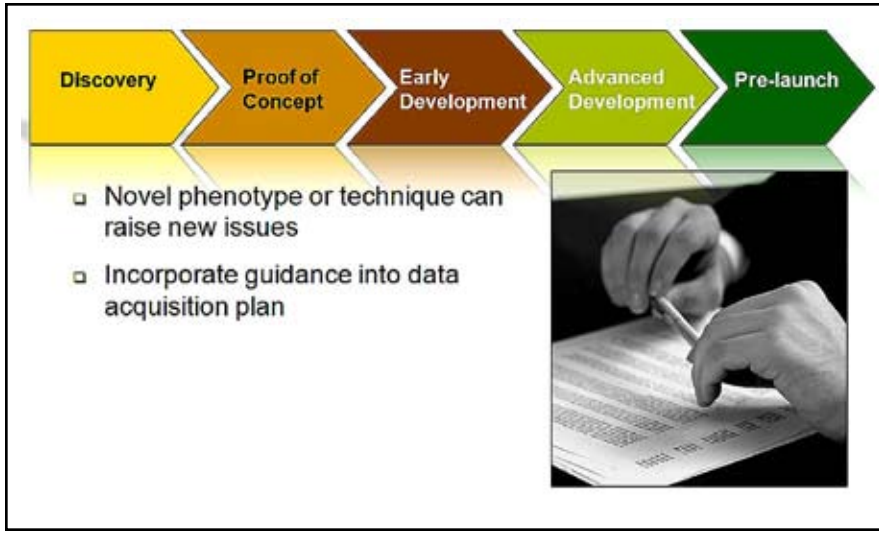

Figure 9. Consultation with regulators.

Analytical Tools

Analytical tools and reagents are a vital part of preparing the "core-package" data for pre-market approval. Consultation with regulators is particularly important if novel methods have to be developed, to produce the right kind and quality of safety data. One also needs to make sure that these methods are validated in the matrix that you're using, and under actual conditions. Good laboratory practices (GLPs) can be expensive. At a minimum, work by contract labs should be conducted with GLPs, including analytical chemistry, animal testing, compositional studies and nutrient analyses. Whether field work is hired out or is performed within an intramural non-GLP research program, it is vitally important to maintain careful records for regulatory compliance.

At each developmental stage, the transformation events created must be screened for various characteristics and only those meeting specifications selected so that they will eventually gain regulatory approval. Approval can be delayed or even derailed because they have not had the appropriate selection.

For regulators, transparency is particularly important. They like to see peer-reviewed literature describing performance and safety of a new trait. It contributes to their familiarity, and it can make their decision making appear not solely based on proprietary company data. Accordingly, publishing results of efficacy and other testing is recommended.

Stewardship

Good stewardship—vital to obtaining pre-market approval of genetically engineered crops—may be thought of internal quality-assurance procedures. Stewardship practices are largely, in my view, internal quality assurance procedures applied at each stage of

development to ensure product integrity throughout the lifecycle. It's important to maintain unique identifiers and meticulous records to ensure that the commercial product is nothing more or less than it is intended to be. Although good stewardship practices cannot eliminate human error or natural phenomena, they go a long way to minimizing events that lead to "front page news"; shortcutting can be costly.

In Summary

The challenges involved in bringing a new genetically engineered crop trait to market can be daunting. There are many possibilities for things to go terribly wrong. Regulatory expertise will not necessarily solve all of the impediments to achieving market success. On the other hand, with careful planning, regulatory approval doesn't have to be an insurmountable impediment.

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His career spans more than 30 years in technical and regulatory service to the food-processing and biotechnology-seed industries. Since 2001, he has helped clients reach their regulatory goals for biotechnology-derived food and energy crops, industrial products, biopesticides and soil additives. He is a co-founder of the Agricultural BioTech Regulatory Network, an international group of independent regulatory professionals serving the agricultural biotechnology industry from product concept to commercialization.

Mr. Thenell earned degrees in bacteriology from the University of Wisconsin-Madison and in regulatory science from the University of Southern California School of Pharmacy.