Agricultural Biotechnology: The U.S. Perspective

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Plants that are genetically modified by "modern" biotechnology (i.e., by the application either of in vitro nucleic acid techniques, or of certain cell fusions) are known as "plant LMOs" (living modified organisms) and can have a range of agricultural, pharmaceutical and industrial end uses. Agricultural biotechnology ("ag biotech" or "green biotech") generally encompasses plant LMOs that are tied to the production of human food and/or animal feed.

In recent years, ag biotech products have become an established component of Americans' food supply, both in supermarkets and when dining out. Moreover, production of certain core bioengineered crops (canola, corn, and soybeans) has steadily increased worldwide, including among small, resource-poor farmers in developing countries. At the same time, the United States has experienced high-profile incidents involving the contamination of conventional agricultural products (including processed foods) either by plant LMOs, or by products containing or derived from such LMOs. And there remains strong, vocal opposition to so-called frankenfoods by significant populations outside the U.S.

Proponents of ag biotech state that it will enhance crops' resistance to insects and blight, and tolerance for harmful herbicides and environmental conditions, with consequent increases in crop yields; improve the nutritional contents and shelf life of foods; and reduce the use of synthetic pesticides. These results, they say, will benefit millions of poor people in developing economies who otherwise are unable to provide adequate and nutritious food supplies to their populations.

Critics contend that there is insufficient knowledge about potential negative health and environmental impacts of plant LMOs, and that the claimed benefits for the world's poor have yet to be demonstrated. They also cite various commercial and institutional impediments to the successful transfer of ag biotech practices to third world settings, including intellectual property disputes and the lack of sufficient technical capacity to implement both plant growing programs and government regulatory oversight.

The genetic modification of plants usually involves the production of new plant proteins. Consequently, evaluations of potential adverse health impacts primarily focus upon possible allergenicity (because virtually all known food allergens are proteins) and protein toxicity. Typically the food safety aspects of these toxicology "end points" are evaluated from the standpoint of "substantial equivalence" between conventional foods and those associated with plant LMOs (that is, if a bioengineered food product shows no increased allergenicity or other toxicity when compared to a "safe" conventional counterpart, scientists may conclude that the bioengineered product also is safe for general consumption). (This type of analysis is generally analogous to relative-risk assessments that often are employed when reviewing chemicals that might result in exposure to the general population.)

Potential adverse environmental impacts of plant LMOs include the long-term effects of gene flow (in the field) between transgenic plants and conventional, nontransgenic plants (including the possible depletion/elimination of heritage or other native plants); the creation of so-called superweeds, which are resistant to insects, unfavorable ambient conditions, and/or synthetic pesticides; possible adverse impacts upon "non-target" organisms (e.g., other plants, butterflies); and, more generally, potential negative impacts upon biodiversity. There is a substantial body of scientific knowledge concerning how to evaluate many of these potential impacts. However, given the range and diversity of such potential adverse consequences, considerable work remains before there will be broad scientific consensus as to analytical and assessment principles and protocols.

Numerous parties have an interest in, or are otherwise affected by, the commercialization of ag biotech products. This in turn gives rise to a wide range of potential disagreements and disputes, many of which are related, at least in part, to health or environmental matters.

The commercial "value chain"—the parties who are involved in bringing commercial ag biotech products from invention to market—include: the "tech providers" (i.e., the relatively small number of companies who have developed and applied specific genetic modifications to particular plant genomes, and who own the intellectual property rights to resulting plant LMOs); seed companies, who produce the seeds for use in growing the modified plants; farmers/growers, who plant the seeds and harvest the plants; commodity companies, who purchase the harvested grains and other bioengineered commodities; and food processors, who produce the finished food products for sale in both

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wholesale and retail markets. Downstream parties include wholesalers and business purchasers of the finished products (e.g., institutions, restaurants, other food servers), grocery and other retail stores, and individual consumers. Other significant actors include lending organizations, consumer and environmental public-interest groups, and government agencies. Taken together, these constitute an extremely broad and diverse mix of organizations that may identify legal issues associated with achieving their goals and resolving problems that arise along the way.

In addition to the commercial and regulatory controversies that typically arise in businesses involving a product chain with numerous links, ag biotech brings to the table at least three elements that both compound and magnify legal disputes: (1) an evolving and controversial technology that implicates consumer products and choice; (2) health and environmental considerations that are not easily defined and resolved on a consensus basis; and (3) economic and political dimensions presented in an international framework that affects businesses and individuals throughout the world. Examples include disputes: (1) within parts of the commercial value chain (e.g., the varying interests of small farmers and large growers); (2) between parts of the value chain (e.g., tech providers vis-à-vis food processors); or (3) involving parts of the value chain and other parties (e.g., consumer groups' litigations, and government civil-penalty and/or injunctive proceedings).

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At the intergovernmental level, strong disagreements among developed nations (or trading blocks) have been manifested in trade negotiations which may lead to more formal dispute proceedings. Thus, the U.S. government generally has been quite supportive of agricultural biotechnology, and the U.S. populace has evidenced general acceptance of biotech food products, including confidence in the oversight of ag biotech activities by federal health and environmental regulators. In contrast, Western European consumers and governments alike have taken a skeptical, and often hostile, view of ag biotech (but not of biotech pharmaceuticals), reflecting cultural differences from Americans over food content and quality, a general lack of faith in government regulatory authorities, and (in some cases) protectionist agricultural and import/export policies. This has led to the enactment of European Union (EU) and national moratoria on the development of new ag biotech products, as well as "process" labeling and content restrictions that focus upon the use of biotechnology per se rather than upon material differences (e.g., concerning health and environmental risks) between bioengineered and conventional food products. These restrictive EU requirements effectively have blocked U.S. parties in the value chain from doing business in Europe, and the U.S. government (at the urging of U.S. business interests) recently initiated formal WTO proceedings to have the EU's restrictions declared illegal.

The resolution of differences between developed and developing nations, although to date not as publicly visible as disputes among developed countries, is perhaps even more significant to the long-term success of ag biotech because such differences often implicate both financial and social welfare considerations. Thus, potential markets throughout Latin America and Asia (and, to a lesser extent, Africa) for ag biotech products present significant opportunities for the tech providers and others in the value chain to realize sound returns on their financial investments; and it is foreseeable that these same products will materially improve those countries' ability to feed their populations and to develop sustainable agricultural practices.

Getting there, however, is a real challenge. Thorny and contentious issues of access and benefits-sharing (i.e., the right of people and institutions in the developing countries to own and otherwise control the application of ag biotech) often conflict with the need for commercial entities to protect their intellectual property in the transgenic products and to obtain meaningful profits. Moreover, national political and economic interests might weigh against the use of ag biotech products in a way that adversely affects large segments of indigenous populations. For example, Zambia forbade the distribution of sorely-needed food aid from the U.S. to severely malnourished people because the grains involved were ag biotech products. National leaders cited concerns about possible adverse health effects, as well as their belief that Zambia's own conventional food products might become contaminated and therefore prohibited from future export into Europe (because of the European Community's moratorium on the growth and import of virtually all biotech products for human consumption).

One hopeful sign that these types of problems are resolvable was the Rockefeller Foundation's announcement earlier this year that it has created an African-based and -led organization to facilitate African countries' access to critical materials and information for the development of sustainable food supplies, including those based upon ag biotech. As a key input to this effort, major actors in the ag biotech value chain will transfer materials and knowledge to African institutions on a royalty-free basis. For their part, the

African organizations will develop new crop varieties, carry out biosafety reviews, set up seed-distribution programs for local farmers, and help develop local markets for surplus production.

Given this disparate mix of parties and issues, a U.S. lawyer who advises a client involved in ag biotech would do well to develop a basic grasp of the economic and political big picture, even though the client's requests for legal assistance typically focus upon particular regulatory and/or commercial matters. In this regard, health and environmental regulatory schemes around the world are in a profound state of flux. In a sense, they all seek to address the types of "risk" considerations that government officials have faced in regulating the development and commercialization of conventional foods, drugs, pesticides and chemical products: (1) Risk Assessment—the scientific evaluation of possible health and environmental risks to potentially exposed populations; (2) Risk Management—the consideration of relevant nonscientific factors in decisions concerning the management of activities involving substances and products (this may include the application of "precautionary" principles); and (3) Risk Communications—the provision of information (e.g., regarding potential health/environmental risks, as well as nonscientific factors such as economic costs and benefits) to various publics, via both voluntary and mandatory means.

National ag biotech regulatory schemes often are structured around three basic elements. First, the products covered may include plant LMOs, products containing plant LMOs, and products derived from (but not necessarily containing) plant LMOs. Second, the activities covered typically encompass experimental work (in both laboratories and test fields), test-marketing activities (to gauge consumer/market acceptance), and full-scale commercialization. And third, the particular regulatory measures (as applied to specific products and activities) may include one or more of the following: analytical testing; health and/or environmental effects testing and evaluation; quality and/or content specifications; labeling requirements; certification obligations; premarket review or product registration; restrictions upon sale, distribution, use and/or disposal; and recordkeeping and reporting requirements. For the practitioner who is asked to advise concerning specific regulatory programs (both existing and proposed), it is useful to dissect such programs along these three lines as they apply to a client's particular fact situations.

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The U.S. Regulatory Framework

In the United States, statutory authority for the oversight of ag biotech products and activities is shared among the Department of Agriculture (USDA), the Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA). In light of this overlapping jurisdiction, in 1986 the President's Office of Science and Technology (OSTP) issued "Coordinated Framework for the Regulation of Biotechnology," a comprehensive policy statement for the regulation of genetically modified organisms (GMOs, which include plant LMOs) and products derived from GMOs. Since the mid-80s, the three agencies have issued various regulations and policy statements that reflect the evolving nature of the technology and our understanding of particular technical matters. The basic jurisdictional boundaries have remained largely the same, however, and there are no prospects on the horizon for Congress to alter the overall statutory setting.

According to the Coordinated Framework, products created using genetic engineering are presumed to be as safe (concerning both public health and the environment) as their conventional counterparts unless evidence indicates otherwise. Thus, the Coordinated Framework provides that federal oversight of GMOs, and of products derived from GMOs, will be based upon existing statutes and regulatory authorities relating to conventional products, and that special review or treatment based upon the fact that a product was created using biotechnology will not be required.

Genetically Modified Plants—Under the Federal Plant Pest Act (PPA), the USDA's Animal and Plant Health Inspection Service (APHIS) regulates genetically modified plants that have been derived from "plant pest" organisms. Plant pests include any plant diseases, bacteria, fungi, viruses, and the like that are new or otherwise not widely prevalent within the U.S. and which, if released, could harm U.S. agriculture.

APHIS has promulgated regulations to protect U.S. agriculture from the risk of an inadvertent release or dissemination into the environment of a plant pest from genetically modified plants. The rules apply both to organisms that have been altered or produced by genetic engineering where one or more of the constituents (donor, vector/vector agent, recipient) comes from a family or genus of organisms that are known to contain plant pests, and to products (e.g., seeds, plants or pollen) that contain such organisms. Regulated activities span the importation, inter-

state movement, and release into the environment of such organisms and products, including both field testing and shipment for commercial distribution and use. Depending upon the particular activity, the responsible party must either provide notice to or obtain a permit from APHIS on an event-by-event basis. However, once sufficient data regarding a particular transgenic plant have been accumulated to demonstrate that it does not present a plant-pest risk, the developer may petition APHIS to deregulate the plant by issuing a certificate of nonregulated status.

APHIS has reviewed notifications and issued permits for field testing and other activities involving a large number of plant LMOs. APHIS also has issued several policy and guidance documents, explaining its regulatory process and reporting the results of its reviews. Earlier this year APHIS published a notice of its intention to impose new conditions for the field testing of plant species that are bioengineered in order to produce nonagricultural compounds (i.e., for pharmaceutical or industrial end-use applications). This followed a contamination incident in which a small amount of so-called biopharmed soybeans, designed to produce a pharmaceutical protein and not intended or approved for food or feed purposes, became commingled with soybeans intended for human consumption. The new APHIS permit conditions are intended to minimize the likelihood that similar commingling or other contamination will occur by imposing limitations on the proximity and growing practices of biopharm plants (and plants that are grown for industrial purposes) in relation to food or feed crops.

Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), EPA regulates certain crops that have been genetically modified for pest resistance. In general, if plants produce substances that are intended to protect the plants against pests and disease, EPA considers such substances to be pesticides subject to FIFRA, whether the pesticidal capabilities evolved in the plants or were introduced either by conventional breeding or by genetic engineering. The agency now refers to such pesticidal substances, including the genetic material necessary for the production of such substances, as "plant-incorporated protectants" (PIPs, previously termed "plant-pesticides").

Pursuant to the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA also is responsible for establishing maximum residue levels, or "tolerances," for pesticides that might remain in or on food. This requirement applies to PIPs as well as conventional pesticides.

Although EPA has considered treating PIPs in a manner distinct from other FIFRA-regulated pesticides, at this time most PIPs require registration pursuant to the standard FIFRA regulations and procedures. EPA promulgated rules in 2001 (first proposed in 1994) governing PIPs, which generally exempt from FIFRA requirements only those PIPs that are derived through conventional breeding from plants that are sexually compatible with the recipient plants. However, if the crop is to be used as a food, this exemption applies only if EPA either has exempted any PIP residues in the food from FDA tolerance requirements, or has determined that no tolerance is required. Further, exempt PIPs remain subject to general FIFRA adverse-effects reporting requirements.

This exemption applies as well to inert pesticide ingredients, provided that residues of the inerts are not found in food at levels that are injurious or deleterious to human health. An inert is a substance (e.g., a selectable marker) that is used to confirm or ensure the presence of the active ingredient(s), including genetic material that is necessary for production of the substance.

Also in 2001, EPA proposed two possible regulatory approaches for PIPs that are derived through genetic engineering from plants that are sexually compatible with the recipient plants. EPA stated that it could exempt all such PIPs from FIFRA requirements (other than for adverse-effects reporting) irrespective of the technique used to incorporate the PIPs into the plants (i.e., the agency would expand the current PIP exemption by dropping the provision that, to be exempt, the PIP must have been derived through conventional breeding). In the alternative, the agency could establish a notification process involving some type of EPA screening to review bioengineered PIPs on a substance-by-substance basis. This approach would strike a middle ground between a general FIFRA exemption for all such PIPs, and the current requirement that each genetically derived PIP must undergo full FIFRA registration review and approval. To date EPA has not issued a final rule incorporating either (or any other) approach.

Foods that contain pesticide residues (including PIPs) are considered to be adulterated under the FFDCA unless the residues are covered by an existing tolerance (established by EPA) or by an exemption from this requirement. Thus, in EPA's 2001 PIP rulemaking, the agency established a regulatory subpart for PIP tolerances and tolerance exemptions, and exempted (from the requirement for a tolerance) residues of nucleic acids that are part of PIPs.

Finally, EPA's 2001 rulemaking clarified the agency's interpretation that the FIFRA registration requirements do not apply to living plants, as distinct from PIPs, which themselves are used as biological control agents. Well-known examples are marigolds, chrysanthemums, and geraniums when planted in gardens in order to protect vegetables from various plant pests. Note that this exemption does not apply to substances that are extracted from host plants and separately applied as pesticides to other plants (e.g., pyrethrum that is extracted from chrysanthemums and applied to other plants). Also, nonliving plants or plant parts are not exempt — such as powder that is produced from

dried and processed plant parts, and that is applied as a pesticide to other plants.

Genetically Modified Foods—FDA has primary authority to regulate genetically modified foods under the FFDCA, which generally does not require pre-market approval of whole foods (e.g., fruits, vegetables, grains) that have long been dietary components and that are "generally recognized as safe" (GRAS). However, any non-GRAS substance that is intentionally added to food is considered to be a "food additive" and is subject to FDA pre-market review and approval.

FDA's food-safety responsibility extends to the regulation of substances that are introduced into plants through genetic engineering where the new plant varieties are expected to become a component of food. Pursuant to a 1992 policy statement, FDA takes the position that, in most cases, substances that are expected to become a component of food as a result of genetic modification will be the same or substantially similar to components already found in conventional foods (e.g., proteins, fats and oils, and carbohydrates). As such, foods derived from genetically modified plants are regulated by FDA within the framework of existing FDA regulations.

In particular, FDA has stated that it will treat such substances as food additives, requiring pre-market approval only when the substances differ substantially in structure, function or composition from substances found in conventional foods. Thus, under FDA's policy, the regulatory status of a food, irrespective of the method by which the plants are developed (i.e., conventional breeding or genetic engineering), depends upon the objective characteristics of the food and not the method by which it is produced.

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Over the years, numerous manufacturers have consulted voluntarily with FDA staff concerning new bioengineered foods, including safety and quality control tests and assessments. FDA in 2001 proposed rules that would formalize this practice by requiring manufacturers of plant-derived, bioengineered foods (and animal feeds) to provide pre-market notifications to FDA at least 120 days prior to marketing such products. The companies would be required to conduct pre-market consultations with FDA staff, and to include in their notifications information and data that show that the foods are as safe as their conventional counterparts. This rule would include foods derived from plants that have been modified to include PIPs. To date, FDA has not finalized these rules.

FDA is authorized to take action against foods that are misbranded because of labeling statements, and FDA in 2001 published guidance for industry concerning voluntary labeling of bioengineered foods. This guidance addressed a number of issues concerning both the content and substantiation of labeling statements. It emphasized that there is no U.S. requirement to include on labels information that particular foods or their ingredients either are bioengineered or are produced from bioengineered food. FDA also discussed the use on labels of such terms as "GMO free" and "not genetically modified," including the need for such statements to be technically accurate, substantiated, and not misleading.

On a more comprehensive basis, the OSTP in 2002 published a notice and request for comments on future actions by FDA, EPA, and APHIS to update requirements for field testing biotechnology-derived food and feed crops. The notice referenced annual increases in the number and diversity of ag biotech field tests, and pointed to foreseeable increases in the likelihood both of cross-pollination from such field tests to conventional commercial fields, and of commingling of seeds from field tests with commercial seeds or grain. According to OSTP, the three agencies will establish a coordinated federal regulatory approach to update ag biotech field test requirements, and to establish early food safety assessments for new proteins produced by plants that are intended for food or feed.

Specifically, FDA plans to propose guidance for addressing possible intermittent, low-level presence in food or feed of new nonpesticidal proteins from biotech-derived food/feed crops. EPA would issue guidance that addresses the process for obtaining the Agency's safety review of low-level intermittent residues of PIPs in food, and guidance for containment controls for experimental field trials. In addition to strengthening field-test controls for non-food uses (e.g., pharmaceuticals), APHIS would amend its regulations to provide criteria for allowing regulated GMOs to be present in commercial seeds and commodities if they pose no unacceptable environmental risk. The timing for these agency actions is unclear.

In sum, the 1986 Coordinated Framework remains largely intact, even as regulatory measures

are taken to deal with specific health and environmental matters in the face of scientific advancements and well-publicized contamination incidents. Thus, it is unlikely that the U.S. regulatory system for ag biotech products will be altered in a fundamental fashion in the foreseeable future.

Liability Considerations

A variety of potential liabilities may face clients depending upon their interests in particular ag biotech products. The most significant adverse consequences generally involve tangible commercial losses and harm to product (and company) reputation.

First, the core U.S. regulatory provisions (implemented by APHIS, EPA, and FDA) involve government review and/or approval of activities that occur at various points in the value chain. Therefore, regulatory noncompliance typically may result in the inability to produce, distribute, and sell both a company's noncompliant regulated product and others' products that are affected by it. This may include otherwise-compliant grain that has been contaminated by noncompliant grain, and processed food products that are derived from plant LMOs. Further, recalls and injunctive measures can be quite expensive and severely damaging to a product's future value. Also, the government may impose civil penalties for activities involving noncompliant products, although monetary penalties can be relatively insignificant when compared to the costs of complying with cease-and-desist orders and other injunctive measures.

Second, failure to comply with regulations may enhance exposure to both contract and tort liabilities. Commercial contracts typically contain terms warranting that the products and services being sold—for example, seeds as the "delivery system" for particular ag biotech applications—comply with applicable statutory/regulatory requirements. In addition, general commercial warranties may be interpreted to include warranties of regulatory compliance. Thus, persons who are found to have violated government requirements may face liability to persons who are in privity downstream, where such noncompliance materially affects the latter's own commercial activities and financial returns.

Third, persons may bring tort claims based upon a number of theories, seeking compensation for damages allegedly caused by others' activities involving ag biotech products (e.g., cross-pollination of one person's conventional crops by another person's plant LMOs). Plaintiffs may find their cases easier to prosecute in the event of the defendants' regulatory noncompliance, because many courts will conclude that such noncompliance constitutes per se negligence. Even in the absence of such a finding, potential tort liability—including product liability class-action litigations—is a major concern to parties in the ag biotech value chain, because of the large number of downstream persons potentially involved with ag biotech products.

In this regard, although health (food safety) and environmental issues have featured prominently in the debate over ag biotech, experience to date indicates the difficulty of basing successful tort actions upon demonstrated adverse health or environmental impacts. Thus, the commercial biotech food crops have not been shown to cause harm to humans, which is not surprising considering that both industry and the U.S. government typically evaluate and approve of such crops only if they are found to be substantially equivalent to conventional (non-biotech) ones. Likewise, although considerable attention is being given by both industry and government scientists to the potential adverse environmental impacts of LMOs, such impacts have not been demonstrated on any significant scale. For the foreseeable future, therefore, successful tort actions most likely will be grounded in property and other commercial damages.

Finally, on a broader scale, the major challenges to proponents of agricultural biotechnology lie outside the U.S.—particularly the inability of U.S. business interests to gain significant access to non-U.S. markets, due either to restrictive or nonexistent regulatory frameworks, or to the lack of meaningful capacity by government officials to manage such frameworks as do exist. Lawyers' involvement in addressing these concerns lies primarily in the policymaking and institution-building arenas, which in turn provide the frameworks within which the various parties' obligations and liabilities will be established.

In sum, the ag biotech field presents an evolving array of client interests and responsibilities that can lead to a host of legal issues and challenges. Many are of type that U.S. environmental lawyers have faced in other situations—particularly those who have experience in the regulation of commercial products, including risk assessment and risk management programs. The technology is here to stay, and will result in a range of interesting compliance and liability matters for years to come.