

Regulatory Barriers to the Development of Innovative Agricultural Biotechnology by Small Businesses and Universities

ABSTRACT

Since the early 1980s, American taxpayers have invested heavily in public, university, and small business developers of crops and foods improved using biotechnology. Yet the return on this investment, in terms of new, improved genetically engineered (GE) crops, is disappointingly thin. Although the U.S. Department of Agriculture, universities, and small businesses have developed dozens of GE crops—with improved traits ranging from healthier and less allergenic to safer and more environmentally sustainable—and carried many through safety and premarket testing, almost all have been denied commercial release mainly because of U.S. regulatory obstacles that disproportionately penalize public, academic, and smaller private breeding entities.

In theory, scientifically sound regulations serve the public good by assuring a reasonable degree of product safety while not unduly stifling innovation. In a scientifically rigorous, risk-based safety assessment, the degree of regulatory scrutiny is commensurate with the degree of identified risk posed by the product in question. In reality, however, our current regulations are not based on product risk, but on spurious, undocumented risks posed by the process of genetic engineering. These regulations impose scrutiny well beyond that imposed on non-GE products posing similar risks. As well, the unnecessarily onerous and expensive regulations discourage and stifle innovation, especially in small businesses and universities.

This report analyses the current U.S. regulatory system for GE crops, compares it with those of major trading partners, and considers various aspects of agricultural biotechnology regula-



Despite foundational contributions requiring considerable public resource commitments for GE crop innovation and development, the academic institutions and small private entities have been almost entirely excluded from the agricultural biotechnology market. (Photo from Lightspring/Shutterstock.)

tion, including labeling and scientifically sound alternatives to the unnecessarily restrictive current regulatory system to allow the benefits of safe agricultural biotechnology products from small business and universities to accrue to farmers, consumers, and the environment.

INTRODUCTION

Recombinant deoxyribonucleic acid (rDNA), a set of techniques also known as bioengineering, genetic engineering

(GE), or genetic modification (GM), was developed in the 1970s and is now used to produce everything from pharmaceuticals to crops and foods with such traits as nutritional enhancements or disease resistance. Although public concerns regarding the GE process for medical or industrial applications have been relatively mute, agricultural applications (“agricultural biotechnology”) elicit fear from vocal segments of society, including many nongovernmental organizations. These fears can often be traced to

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the large knowledge gap separating the science from nonscience segments of society. There is a clear consensus in the scientific and medical communities, however, that GE crops and foods are at least as safe as corresponding conventionally bred crops and foods. In the nearly half a century since its inception, not a single case of harm attributed to a GE modification has been documented.

Safety regulations governing GE processes were initiated after the scientific community itself raised concerns that the powerful new technology could potentially create unforeseen risks (Berg et al. 1975). Robust scientific studies conducted over the past five decades, however, have revealed that introduction of genetic variation into plants using the GE process is unlikely to generate risks beyond those inherent with conventional breeding methods (e.g., see NRC 1983, 1987; NRC/IOM 2004; OECD 1986). This position of safety held by the science community since the mid-1980s is reflected in the statements made presciently and explicitly by the U.S. National Academies of Science:

- There is no evidence that unique hazards exist either in the use of [rDNA] techniques or in the transfer of genes between unrelated organisms.
- The risks associated with the introduction of [rDNA] engineered organisms are the same in kind as those associated with the introduction into the

environment of unmodified organisms and organisms modified by other genetic techniques (NRC 1987).

Nevertheless, many jurisdictions eschewed the global scientific consensus and imposed strict safety regulations, arguing that the lack of familiarity with the GE process justified stringent regulatory oversight (OSTP 1986) and that such regulations would help foster public acceptance of the technology. Those regulations, promulgated in the United States, Canada, and the European Union (EU) between 1986 and 1994, serve as the foundation of agriculture and food biotechnology regulations today. Given the past 30 years of experience with genetically engineered (GE) plants in open field cultivation, and commercialized GE crops grown on billions of acres worldwide since 1996, the scientific predictions on the safety of the process have been validated. This validation is exemplified by a 2014 metastudy of more than 1,700 peer-reviewed papers covering the spectrum of GE crop and food safety that demonstrated the lack of evidence of new risks or harms (Nicolia et al. 2014). A more recent comprehensive analysis conducted by the U.S. National Research Council (NRC) confirms and extends these findings (NRC 2016). Clearly, the process of GE is at least as safe as traditional methods of breeding.

Much of the enabling technology for agricultural biotechnology was developed

in academic or other public institutions, going back to the initial rDNA technology itself by Herb Boyer and Stanley Cohen at the University of California–San Francisco and Stanford, respectively (Cohen et al. 1973). Many of the earliest field trials with GE plants were conducted by the public sector (especially the U.S. Department of Agriculture [USDA]) and academics at various universities, and some of the earliest commercialized crops receiving regulatory approval were from academia (viz. papaya: Gonsalves 1998, USDA–APHIS 1996 [and subsequent documents], USFDA 1997a; viz. flax: McHughen et al. 1997, USDA–APHIS 1999 [and subsequent documents], USFDA 1998).

Despite foundational contributions requiring considerable public resource commitments for GE crop innovation and development, the academic institutions and small private entities have been almost entirely excluded from the agricultural biotechnology market. Today, there are still only three GE crops from public institutions approved in the United States, only one of which was approved in the past 20 years (see later). The cost of regulatory compliance—calculated at from \$7 to \$15 million for each event¹

¹ An “event” refers to one DNA (deoxyribonucleic acid) segment inserted into one genome. Each time DNA is inserted into a genome, the resulting plant (and crop) is known as a particular “event.”

(Kalaitzandonakes, Alston, and Bradford 2007) to more than \$30 million (of a total development cost of \$136 million for each new GE variety), according to industry surveys (McDougall 2011)—is mainly responsible for the lack of GE products entering the marketplace developed by public sector and smaller companies (Miller and Bradford 2010). The current regulatory barrier is depriving society of the vast benefits of its considerable investment in public entities and small company-derived GE products. Hence a revision of these regulations to center on the product, rather than the breeding process, will enable innovations from public institutions and smaller businesses to benefit society and the environment.

Given the current U.S. agencies' ongoing review of agricultural biotechnology regulatory policies, now is the time to fundamentally reprogram these oversight procedures to recognize familiarity, knowledge, and experience gained, and to efficiently meet their primary public policy purpose of providing reasonable assurance of product safety without unduly stifling innovation and competition.

BACKGROUND AND HISTORY OF AGRICULTURAL BIOTECHNOLOGY REGULATION

The primary goal of regulations is to assure safety. Safety, in this respect, falls into two general categories: GE foods and feeds must be “as safe as” counterpart non-GE versions, and they must not cause additional environmental problems.

The initial regulations governing rDNA were aimed at health and medical applications (NIH 1976, 1978) but were subsequently extended to agricultural biotechnology (Prado et al. 2014; Wozniak and McHughen 2012).

The United States agricultural biotechnology regulatory history is covered in depth in the Status of U.S. Regulatory Structure section. Briefly, in 1986 the White House's Office of Science and Technology Policy (OSTP) published the Coordinated Framework for the Regulation of Biotechnology (CF). The CF covers the three relevant federal regu-

latory agencies (USDA, Food and Drug Administration [FDA], and Environmental Protection Agency [EPA]), which together are responsible for the safety oversight of agricultural biotechnology products in the United States (OSTP 1986). Early in the development of agricultural biotechnology regulations, new or separate legislation was not necessary because existing statutes and resources were deemed sufficient to provide and enforce regulations.

Several jurisdictions have since reviewed their agricultural biotechnology regulatory structure, but the changes made have often increased stringency despite the increased familiarity with the safety of the GE process. For example, in 2001 the EU updated the “GMO” (genetically modified organism) regulations drafted in 1990 under 90/220/EEC (which included rDNA and other techniques that it mistakenly believed “could not occur in nature”), which simply exempted *Homo sapiens* from the definition of GMO. This was partly because human in vitro fertilization, practiced since the 1970s, arguably designated those resulting human babies as GMOs (McHughen 2016).

Benefits of Agricultural Biotechnology

There is ample evidence that GE in plant breeding is of benefit to farmers, to consumers, and to the environment (Barfoot and Brookes 2014; Brookes and Barfoot 2017a,b; CAST 2016; Green 2012; ISAAA 2006; Klümper and Qaim 2014; Mannion and Morse 2012; NRC 2016; Qaim 2009). These documented benefits include higher yields (which result in less expensive foods); cleaner crops (less dockage for farmers and higher quality for consumers); increased incomes for farmers; less pesticide use; and substitution of more benign pesticides for older, more toxic, and environmentally damaging pesticides.

Other environmental benefits include reduced topsoil loss with some GE crops facilitating no-till and reduced tillage production. Klümper and Qaim (2014) concluded that “. . . on average, GM (i.e., GE) technology adoption has reduced chemical pesticide use by 37%, increased

crop yields by 22%, and increased farmer profits by 68%. Yield gains and pesticide reductions are larger for insect-resistant crops than for herbicide-tolerant (HT) crops. Yield and profit gains are higher in developing countries than in developed countries.” These documented beneficial outcomes have been accompanied by relatively few negative outcomes (e.g., the incursion of weed resistance to corresponding herbicides [NRC 2010]). Such negatives, however, are not exclusive to GE agriculture (evolution of pesticide resistance is well documented in traditional, non-GE, agriculture), and GE crops do not increase the problem. Indeed, recent findings show GE herbicide resistant crops decrease the problem by displacing older herbicides that are more prone to generate resistant weeds (Kniss 2017). Nor are they safety issues; they are instead agronomic management issues.

Farmers obviously see benefits, given the more than 90% adoption rate among U.S. corn, soy, and cotton farmers, who voluntarily choose to grow GE varieties each year. When the USDA surveyed farmers, asking why they choose GE varieties, farmers said that GE crop benefits include higher yields (resulting in higher incomes), reduction in pesticide use, and more flexibility in managing weeds and other pests (Fernandez-Cornejo et al. 2014).

Furthermore, the net reduction in pesticide use and safer foods (via reduction of mycotoxin content grains, especially Bt² corn)—as well as major environmental benefits, the preservation of topsoil, and reduction in greenhouse gas emissions (Brookes and Barfoot 2015; NRC 2016)—are outcomes consumers support (Betz, Hammond, and Fuchs 2000; Wu 2006; Wu, Miller, and Casman 2004) but often don't appreciate, given the disconnect between the general public and agricultural community. Additional benefits not well communicated by the agricultural community to the consumers include increased crop productivity and quality (fewer weeds and thus less dockage), which helps keep food prices down.

² “Bt” refers to any of several genes and corresponding insecticidal proteins originating in *Bacillus thuringiensis*.

Ironically, even farmers who chose not to grow GE varieties benefit from the technology. For example, producers of non-Bt corn benefit economically from neighbors who grow Bt corn due to the Bt technology lessening insect pest pressure in the local region, thereby decreasing spray applications by the non-Bt adopters (Hutchison et al. 2010).

These documented benefits are attributed mainly to large-acreage GE field crops (i.e., corn, soybean, cotton). There are few corresponding benefits attributable to smaller and specialty crops, because GE versions of smaller (including horticultural and forestry) crops—predominantly bred by public academic and smaller private entities—are virtually nonexistent, primarily because of regulatory barriers. Thus, these and other prospective benefits of GE crops are denied to farmers, consumers, and the environment. Yet these forgone benefits are usually ignored in regulatory assessments.

Do New Breeding Techniques Warrant Regulatory Oversight?

In contrast to “traditional” GE, in which chimeric DNA segments from diverse sources are fused together and inserted into a host plant cell using *Agrobacterium* or other gene transfer agents/mechanisms, new breeding techniques (NBTs) use recently developed technologies to modify or “edit” endogenous DNA, resulting in an alteration of gene expression or function. These new “genome editing” techniques include Zinc finger, TALENs, and CRISPR-CAS9 (Abdallah, Prakash, and McHughen 2015).

The current GE process-based³ regulations used in most jurisdictions were initially defined in the 1980s. These regulations are triggered by the use of certain techniques or processes developed

in that era—especially rDNA—to create a “transgenic” organism(s). Subsequent revisions to the definitions did not keep pace with advances in technology or with knowledge gained from studies conducted with early transgenic plants. At least some NBTs appear to be outside the scope of authority of current regulations (Camacho et al. 2014). Although genome editing techniques are all distinct, a common feature is that they do not require gene transfer from other species and they do not necessarily leave inserted DNA fragments in the resulting genome. Such NBTs may not fall under regulatory oversight if they do not involve genetic material from, for example, “plant pests” (USDA) or the transfer of “foreign” DNA “across the ‘species barrier’” (EU).

Examples already exist. Waltz (2016) claims that approximately 30 recent GE plants did not trigger USDA regulatory scrutiny. Pacher and Puchta (2017) list an additional 12 such examples, including novel potatoes, mushrooms, corn, and wheat.

New breeding technologies can mimic changes in the DNA identical to those resulting from historical, unregulated technologies such as induced mutagenesis that are considered to pose no unreasonable risk; products from NBTs cannot be deemed inherently risky. Differential regulation of products of similar risk (e.g., induced mutagenesis vs. NBT) would violate the longstanding regulatory maxim that items of similar risk warrant the same degree of regulatory scrutiny.

Agricultural Biotechnology Innovations in Academic Institutions and Small Businesses

Since the mid-1980s, U.S. taxpayers have invested substantially in agricultural biotechnology research and development in USDA, academic, and small private labs to provide more sustainable, safe, and efficient foods and crops. These public and smaller private entities have developed a broad range of GE crops, from apples to zucchini, with new and useful traits ranging from enhanced biotic and abiotic stress tolerance to nutritional improvements (Miller

and Bradford 2010; Parisi, Tillie, and Rodríguez-Cerezo 2016; Ricroch and Hénard-Damave 2016). More than 20,000 regulated field trials have been approved by the USDA since the first approved field trials conducted in 1987 (USDA–APHIS 2017a). These include almost a thousand different GE-derived events in small market and specialty crops developed by public and small private entities (Miller and Bradford 2010). In spite of the large public investment, early technical successes, and promising field trial results, only two GE crops developed in public institutions have been commercially released—the previously mentioned virus-resistant papaya (Gonsalves 2004) and the short-lived bioremediation flax (McHughen et al. 1997). Both of these were developed in the late 1980s and released in the mid-1990s.

More recently, a GE plum pox virus-resistant plum developed by USDA–ARS (Agricultural Research Service) successfully passed U.S. regulatory clearance but has not been commercialized (Scorza et al. 2013). “Orphan” GE specialty and small-market crops are those developed in public and small-company labs, often funded from public sources but never commercialized—not because of safety issues or failure of the traits, but because of insurmountable regulatory obstacles. These are very sparse returns, and the lost opportunity costs from not taking advantage of the benefits of the GE traits are substantial (Graff, Zilberman, and Bennett 2009), especially considering the substantial public investment in agricultural biotechnology over thirty years.

STATUS OF U.S. REGULATORY STRUCTURE

In the United States, agricultural products of biotechnology are regulated under the CF using existing laws to assess rDNA organisms (OSTP 1986). Regulation under the CF is commonly considered to be product focused, but it actually has a de facto process-based trigger, namely the use of rDNA techniques. The USDA, EPA, and FDA are the principal agencies evaluating GE crop safety. These agencies address, respectively, potential effects on agriculture, the

³ A process-based regulation regulates a product based on the way it was made, rather than on the features of the product itself. As an example, a GE plant made with a gene gun might not be regulated, whereas the same GE crop made using *Agrobacterium* would be regulated. In contrast, a product-based regulatory system would look at the safety of the product features—if there is a cause for concern—regardless of the method used to make it.

environment, and human/animal health. Thus, depending on the crop and trait, one, two, or all three of these agencies may independently regulate a crop. The statutes, regulations, and processes for regulatory-compliant risk assessments for GE crops in the United States are described in detail elsewhere (McHughen and Smyth 2008; Wozniak and McHughen 2012).

U.S. Department of Agriculture

The USDA Animal and Plant Health Inspection Service (APHIS) is charged with protecting U.S. agriculture from pests and diseases under the authority of the Plant Protection Act, and it provides procedural oversight of the release into the environment and interstate movement of GE organisms, designated as “regulated articles.”

Statutory authority for regulation by USDA–APHIS initiates when the derived product is produced using a pathogen (e.g., *Agrobacterium tumefaciens*) or contains DNA from pathogens. The legal premise is that pathogen genomic fragments might in some way convert the recipient plant into a plant pest, and thus the recipient must be evaluated to ensure it has not acquired new plant pest characteristics. Once it has been demonstrated that the GE crop has not acquired plant pest features, it can be deregulated through a petition process. Once deregulated, the previously regulated products are no longer subject to oversight by USDA–APHIS.

The plant pest criterion, a contrived and scientifically baseless premise, not only limits the scope of what APHIS can evaluate, but it leads to incongruous results. For instance, plant transformation involving synthetic or nonpathogen-derived DNA introduced by biolistics is not subject to regulatory consideration by APHIS. In contrast, an identical product created using *Agrobacterium* is subject to regulation. As a practical example, the introduction of the Xa21 bacterial blight disease resistance gene from a wild relative into cultivated rice was conducted using both traditional crossing and rDNA. The resulting rice plants both carried the identical Xa21 gene, but the GE version was shelved because of the necessity

of extensive and expensive regulatory approvals triggered by the presence of a promoter fragment (CaMV-35s) from a plant pathogen, cauliflower mosaic virus. The “traditionally bred” version could enter breeding programs and commerce with no regulatory oversight whatsoever (Khush, Brar, and Hardy 2001; McHughen 2016; Tu et al. 1998) and is now being grown on more than five million acres in India and Bangladesh (Xu, Ismail, and Ronald 2014). The resulting two rice lines were phenotypically identical, and thus whatever risk posed by one was equally posed by the other. In this case and many others, regulatory oversight was based on the nonscientific “process” trigger (of using rDNA to transfer the “plant pest-derived” CaMV-35s promoter) rather than on the risks posed by the features of the products themselves.

Since 2004, APHIS has seen a steady stream of inquiries, especially regarding products derived through NBTs. Recently, USDA–APHIS provided some clarification of regulatory incongruities posed by gene editing methods through inquiries submitted through the “Am I Regulated?” portal in which APHIS responds to *Regulated Article Letters of Inquiry* regarding the regulatory status of proposed products (USDA–APHIS 2017b).

Responses to date to these inquiries indicate that the USDA lacks the statutory authority to regulate any item from which the rDNA has been removed (Wolt, Wang, and Yang 2016). Instances involving small template or directed transgene insertions would appear to remain of regulatory interest, depending on the source of the template DNA (Camacho et al. 2014). In at least one instance, an *A. tumefaciens* introduction of rDNA was not of regulatory concern when transgenic elements were removed and not present in the final product (USDA–APHIS–BRS 2015).

In this latter case, however, USDA–APHIS agreed that the plant did not fall under its current regulations based on a simple letter from the breeders asserting that there were no *Agrobacterium* elements (or other plant pathogen components) remaining. Despite the lack of any documented risk posed from any remaining *Agrobacterium*-derived DNA

sequences, nothing precludes USDA–APHIS in the future from arbitrarily requiring a full dossier, perhaps equivalent to a deregulation dossier, to provide such assurance.

Because USDA–APHIS approvals of GE crops are considered to be major regulatory actions, USDA–APHIS must also comply with the National Environmental Policy Act. In addition to determining the plant pest status of GE crops, USDA–APHIS conducts an environmental assessment for each GE crop. As long as there are no issues identified, USDA–APHIS will issue a finding of no significant impact statement. Otherwise, USDA–APHIS must prepare a full environmental impact statement, adding months if not years (and dollars) to the approval process.

Whether USDA–APHIS views NBT crops involving simple insertions/deletions with limited numbers of bases and the absence of transgenic elements in the finished product as worthy of regulation is a separate question discussed later in the section on recent OSTP activity.

Food and Drug Administration

The FDA is responsible for safety of food and feed products under the authority of the Federal Food, Drug, and Cosmetic Act (FFDCA). The FDA maintains a scientifically sound product focus for GE crops (but not for GE animals; see later) and has long maintained a position that foods and feeds derived from rDNA technology are as safe as counterpart non-GE foods and feeds. The FDA evaluates the safety of GE crops and derived foods and feeds through a consultation evaluating the compositional equivalence of the GE product and comparable non-GE varieties. Special attention is given to potential anti-nutrients (especially food-borne allergens and toxins) and changes to nutritional composition. The FDA consultation is completed when it has “no further questions”—i.e., the GE product has been shown not to have any material safety differences from the non-GE version, and it is therefore “as safe as” the corresponding non-GE product.

A premarket notification procedure was suggested by the FDA in response to public interest in a more transparent

safety evaluation for GE-derived foods and feeds (USFDA 1997b). Although the suggestion was not codified in law, every GE crop brought to market has undergone this premarket consultation; so in practice this “voluntary consultation” is, in reality, mandatory.

Whereas the FDA has based its regulation of plant biotechnology closely on science, the same is not true of its regulation of rDNA in animals. Instead, the FDA defines animals created using rDNA to be “pharmaceuticals” and requires the animals to meet standards designed for pharmaceutical chemicals. This criterion may have contributed to the 18 years it took for the FDA to approve the AquAdvantage™ salmon carrying an rDNA construct that was first developed in 1989 (Ledford 2015). The regulatory compliance costs amounted to more than \$60 million. Such a high cost to achieve regulatory approval obviously discourages the development of improved GE animal varieties by public sector scientists and small companies.

When using gene editing tools to delete a DNA segment (e.g., to generate hornlessness in Holstein cows [Carlson et al. 2016]), the FDA definition implies that the deletion of DNA would be deemed a pharmaceutical. Even more bizarrely, if that allele were to be segregated away from the recipient animal via traditional breeding, the absence of that deletion in the offspring would be now classified as a “chemical residue.” Furthermore, in a request for comments on proposed regulation of rDNA animals (Docket No. FDA-2008-D-0394-0279), the FDA asks for suggestions on how to refer to “genetically engineered” animals, proposing to call them “animals whose genomes have been altered intentionally” and later suggesting the term “intentionally altered animals.” But these terms accurately describe the products of conventional breeding, which are not regulated.

The designation of “human intentionality” and the presumption by the FDA to be an increased safety risk is not language grounded in science. For example, if a swine breeder intends to introduce a targeted genetic variant at a locus for a deliberate outcome, using prior knowledge to support such a variant would translate to the expected pheno-

type; this would be construed as a greater safety concern than if the same desired trait appeared by random chance or by mutagenesis. A scientist/developer would face an ethical dilemma in answering a question in a regulatory dossier asking if the expected phenotype in the product was created intentionally, knowing that an affirmative answer would mean more than a decade of regulatory scrutiny at a huge financial cost, whereas the same product created serendipitously would apparently be considered safe.

Environmental Protection Agency

The EPA regulates pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the amount of pesticide residues in food and feed under the FFDCFA, and microbes engineered for nonpesticidal purposes through the Toxic Substances Control Act. The EPA also regulates plant-incorporated protectants (PIPs), which are defined as pesticidal substances produced in plants, including the genetic material necessary for their production. Under FIFRA, a pesticide is defined as a substance intended to “prevent, destroy, repel or mitigate a pest.” Under this broad definition, the EPA considers the DNA or genetic material for a pesticidal substance itself to be a pesticide because of the intent of producing a pesticidal effect.

Pesticides are also subjected to a registration process, with accompanying fees and ongoing reporting. Plant-incorporated protectants are thus deemed “pesticides.” This aspect of regulatory oversight and registration is applied equally to chemical pesticides and to PIPs. The consequence of this language within the current regulatory system has caused controversy and adds significantly to the expense of developing GE crops for disease resistance. If a substance meets the definition of a PIP (with intent to prevent, destroy, repel, or mitigate), even if the gene product is not toxic, it must undergo the elaborate, time-consuming, and costly EPA registration process.

Environmental Protection Agency regulations are also process based, because only those pest resistance traits incorporated using a GE process are regulated.

Genetically engineered crop assessment within the EPA is intended to regulate the pesticidal property rather than the crop itself. For instance, a GE Bt-containing crop is evaluated principally through assessment of the PIP (the expressed Bt protein), provided the transformed crop otherwise shows similarity (in weediness and outcrossing potential) to the non-transformed counterpart.

This classification of fragments of DNA, nucleotides, and genes as pesticides has created its own set of incongruities, reviewed in Conko and colleagues (2016). Genetically engineered crops with pesticidal properties must be reregistered as pesticides at periodic intervals, and the seed or nursery stock must bear a pesticide label. Fines have been imposed on companies importing seeds from winter nurseries when these have not had their proper pesticide import permits. Not surprisingly, only three crops engineered for disease resistance have managed to receive EPA approval (viz. papaya, plum and potato), despite the ease with which resistance genes can be transferred or edited. In contrast, the multitude of disease-resistant crops developed using traditional breeding methods faced no premarket regulatory review.

Recent Office of Science and Technology Policy Activity

In recognition of the rapid pace of biotechnology innovation and its importance to advancing the bioeconomy, the OSTP issued a memorandum to the heads of the three biotechnology regulatory agencies to update the CF. Three goals were cited: (1) clarify current regulatory roles and responsibilities; (2) develop a long-term strategy to ensure that the federal regulatory system is equipped to efficiently assess risks, if any, of future products of biotechnology; and (3) commission an expert analysis of the future landscape of biotechnology products (OSTP 2015).

An interagency Biotechnology Working Group was organized and several documents were developed to address the three goals:

1. *Modernizing the Regulatory System for Biotechnology Products* outlined current agency oversight and responsibilities (USEPA 2017).

2. *National Strategy for Modernizing the Regulatory System for Biotechnology Products* outlined priorities for ensuring that the regulatory system is equipped to efficiently assess risks of future products (OSTP 2016).

3. *Future Biotechnology Products and Opportunities to Enhance Capabilities of the Biotechnology Regulatory System*, commissioned by the interagency working group and conducted by the NRC of the National Academy of Sciences, reviewed original literature on GE crops and concluded that there was no substantiated evidence that foods from GE crops were less safe than foods from non-GE crops (NRC 2016).

The updated framework was released on January 4, 2017 (USEPA 2017). Little policy change resulted from that review, which mainly reiterated the current practices and compiled them into a single document. Arguably, this updated policy did not meet the stated goals of the OSTP memorandum, which were to “increase public confidence in the regulatory system and to prevent unnecessary barriers to future innovation and competitiveness by improving the transparency, coordination, predictability, and efficiency of the regulation of biotechnology products while continuing to protect health and the environment.”

Perhaps the most important statement was that the “(f)ederal agencies that regulate biotechnology products should strive continually to improve predictability, increase efficiency and reduce uncertainty in the regulatory processes and requirements.” In addition, the regulatory system should not impose unnecessary costs and burdens on small and mid-sized companies and academics (USEPA 2017).

REGULATORY STRUCTURES OF IMPORTANT TRADING PARTNERS

The export market, and its labyrinthine maze of regulations, remains an immense barrier to commercialization of GE crops and foods, especially to smaller companies and academics not familiar with the export structure and documentation requirements.

Compounding this difficulty is little international harmonization of dossier requirements, particularly for environmental risk assessment (Bartholomaeus et al. 2015). This necessitates compiling separate dossiers for each market, even for those in which the underlying safety data requirements are identical.

Assessments to ensure food and feed safety are, with some minor variation, standard worldwide, because human physiology and bodily response to toxins and other anti-nutritional factors are predictably uniform worldwide. Potentially hazardous foods are indicated by the presence of specific substances (regardless of the process by which they appeared). The Organisation for Economic Co-operation and Development (OECD) and *Codex Alimentarius* (CAC 2017) provide the scientific foundation, and the tools, to assess safety of foods and feeds. Member states of the World Trade Organization (WTO) are required to adhere to these international standards, and any product deemed safe under Codex standards should be considered safe worldwide. But many countries routinely ignore them, insisting on performing “safety” tests of their own design, which—aside from being superfluous—may not be as scientifically sound. Therefore, the diverse requirements in different countries are significant trade barriers.

European Union

The first legislation in the EU on deliberate release into the environment of GMOs was Council Directive 90/220/EEC in 1990, subsequently amended. The current EU regulatory framework for GMOs and derived foods and feeds is based on a number of directives, regulations, decisions, and guidance documents in which the primary objectives are internal harmonization and protection of human health and the environment. Unfortunately, the EU regulations are characterized by an ambiguous definition of GMO (see later), an expeditiously flexible interpretation of the “Precautionary Principle,” and an unnecessarily comprehensive case-by-case approach to environmental risk assessment, even in the absence of any scientifically documented threats to human health or the environment.

Directive 2001/18/EC lists (1) processes of GM (Annex IA, Part 1); (2) processes that are not considered to result in a GMO (Annex IA, Part 2); and (3) processes that yield GMOs but are excluded from regulation according to the directive (Annex IB). The provided definition of “GMO,” however, is open to interpretation. According to the directive definition, a GMO is (in part) “an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.”

Furthermore, all methods used to alter the genetic material in agricultural biotechnology are known to occur in nature. Recently, Kyndt and colleagues (2015) showed that ordinary sweet potatoes naturally carry remnants of *Agrobacterium* DNA, demonstrating that nature does indeed transfer DNA “across the species barrier” and even uses *Agrobacterium*—a commonly used DNA delivery vehicle in making GE plants. The assumption that gene transfer from one species to another is unnatural, or that the results are of higher risk than “traditional breeding,” is biologically incorrect.

The EU trigger for regulation is based on the presence of foreign recombinant nucleic acids in the final product, according to most current interpretations (Jones 2015; Voytas and Gao 2014). Other experts argue that a combination of process and product is necessary to define a GMO, given that a number of techniques are indicated that do or do not lead to GMOs, while at the same time the product needs to contain recombinant nucleic acids to be a GMO—implying that only “artificially modified” products containing recombinant nucleic acids are encompassed by the regulation (Kahrman, Börneke, and Leggewie 2017; Sprink et al. 2016).

Directive 2001/18/EC on the deliberate release into the environment of GMOs also outlines the authorization procedure and introduces compulsory labelling and postmarket monitoring requirements as well as a public consultation process (European Parliament/European Council 2001). The enabling Regulations (EC) 1829/2003 (European Parliament/European Council 2003a) and (EC) 1830/2003 (European Parliament/European Council 2003b) provide details

on GMO food and feed, as well as traceability and labelling, respectively. The European Food Safety Authority plays a central role in evaluating the risk assessments, using guidelines based on *Codex Alimentarius* (CAC 2017) and OECD standards. Authorizations are limited to a ten-year period, after which authorization renewal is needed (Schauzu 2013).

In the EU, all intentional use of an authorized GMO and its derived product(s) requires labelling when introduced into the market. Adventitious and technically unavoidable presence of material derived from an authorized GMO also requires labelling if it exceeds 0.9 percent, below which no labelling is necessary. If a GMO or its derived product(s) is not authorized in the EU, however, a zero tolerance applies, which is a great cause of concern for many international trading partners.

The EU also tends to invoke and implement the “Precautionary Principle” ambiguously. For example, EU regulations capture GMO Bt corn, but not non-GMO corn, even though Bt corn is demonstrably and unequivocally safer because of its decreased mycotoxin content (Folcher et al. 2010; Wu 2006; Wu, Miller, and Casman 2004). Furthermore, because the non-GMO European corn crop was unable to meet the safety tolerances set in 2005 for fumonisin contamination, the European Commission (EC) conveniently raised the tolerances “to prevent market disruptions” (European Commission 2007) rather than permit more GMO corn to be produced.

The EU policies are also implemented in a contradictory manner. It has authorized a large number of GE events for food and feed import and consumption, but currently only one GE crop event (MON810 corn) for cultivation, leading to a situation in which many GE products are imported that EU farmers are prohibited from producing. More recently, Directive 2015/412/EC, which allows individual member countries to prohibit the planting of GMO crops approved by the EU, seems to violate WTO provisions guaranteeing (1) an undivided EU seed marketplace for imported goods, and (2) the requirement for scientific evidence of novel hazard to justify trade restrictions. The courts will ultimately deter-

mine whether or not Directive 2015/412/EC is legal and enforceable. In any case, Directive 2015/412/EC continues the habit in some EU countries of using non-scientific grounds to deny the substantial benefits of GE crops to EU breeders, farmers, and consumers. Preventing only Swedish farmers access to GE HT sugar beet, canola, and late blight-resistant potato results in an estimated US\$32.5 million of foregone benefits annually (Fagerström and Wibe 2011). Translated to an EU-wide level, this would mean about US\$2.36 billion foregone annually for just these three crops.

Even without WTO conflicts, Directive 2015/412/EC indicates the considerable inherent tension among several member states regarding the GMO governance framework as they try to balance diverging national interests with the goal of reaching a harmonized European position. Casacuberta, Nogue, and du Jardin (2017) listed a number of contentious issues between actors and values in GMO risk assessment and management, including (1) the balance between the EU centralized power and member states; (2) the balance between consistency and the case-by-case approach, and (3) the difficulty of dealing with uncertainty in the risk assessment, which is carried out by scientific experts, while simultaneously delivering a clear message to risk managers.

The EU is also having difficulty grappling with regulation of products arising from NBTs. A number of technical reports and position papers have been published over the years, starting with the establishment of an EC New Techniques Working Group in 2007 (NTWG 2012) and more recent comprehensive reports on genome editing from the European Academies Science Advisory Council (EASAC 2017) and on NBT from the High-Level Group of the Scientific Advisory Mechanism to the EC (EC/HLG–SAM 2017), as well as from academics (Custers 2017). The influential EASAC report, for one, recommends that genetic modifications using NBTs should not fall under the scope of GMO regulations if they do not contain DNA from an unrelated organism. Other reports emphasize that, in order to be defined as a GMO, a product needs to contain detect-

able rDNA. This latter position has been adopted by several EU member states, including Sweden, Finland, Germany, the UK, Ireland, and Spain. A recent request by the United States-based company Cibus on NBT-modified canola compelled the EC to point out that no commercial application is allowed in any EU member state prior to legal clarification at the EU level (Fladung 2016). The status of this anticipated legal clarification is expected in a ruling of the Court of Justice of the EU on mutagenesis in 2018 (Glas and Carmeliet 2017).

It is particularly disingenuous for the EU to claim its regulations are designed to serve public and environmental safety, yet place the greatest regulatory burdens on GMOs, when their own EU-sponsored research studies conducted over a quarter century by more than 130 public scientific teams—costing EU taxpayers more than 270 million Euros between 1985 and 2010—failed to provide any evidence of any increased risk from GMOs (European Commission 2010; Kessler and Economidis 2001).

Canada

Canadian authorities also set regulatory policy early, with the federal government establishing various panels to advise on biotechnology regulation starting in 1977, followed by more detailed reports in 1986 on coordination of the country’s three primary relevant agencies—Agriculture, Environment, and Health (Henley 1987). This group later published *Bio-tech: Regulations—A User’s Guide* (Government of Canada 1988) to advise academics and industry of the nascent rules in 1988. A crucial turning point in international regulatory policy, however, came in 1988 with the Canadian Agricultural Research Council (CARC) workshop, which brought together expert scientists, regulators, and policymakers from Canada, the United States, and Europe to hammer out scientifically sound regulatory policy (Hollebone 1988; McHughen 1988).

The CARC meeting took seriously the scientific advice from the OSTP (1986), OECD (1986), and NRC (1987) as a foundation for scientifically sound regulatory policy. Presciently, the discussion

anticipated concepts like cisgenics⁴ (a term not coined until years later) and the realistic potential for unintended transfer of allergens, proved several years later by Nordlee and colleagues (1996) with a gene for allergenic Brazil nut protein transferred to soybean. The regulatory theme “product, not process” did not originate here, but it was clearly heard by policymakers, and that led directly to Canada’s “plant with novel traits” (PNT) policy, which triggers regulatory oversight based on the novelty of the plant and its traits, rather than—as everywhere else—the process (GMO, GE, or rDNA) by which the plant was bred.

Canadian policymakers, like counterparts in the United States, recognized that current statutes were sufficient to regulate products of biotechnology and thus avoided passing new laws and establishing new bureaucracies. Initially, the federal departments of Agriculture and Agri-Food Canada, Health Canada, and Environment Canada handled crop and food biotech issues under their respective statutes. In 1997, however, the Canadian Food Inspection Agency (CFIA) was carved out of Agriculture and AgriFood Canada to separate the research function from the regulatory function of that large department. Today, the CFIA administers environmental releases and feed safety issues with PNTs, whereas food safety regulations are administered by Health Canada. Environment Canada serves as the “failsafe,” capturing any “new substances” (including PNTs) that are not regulated by either the CFIA or Health Canada.

Although Canada’s PNT policy is often hailed as the “scientifically sound” example for others, the policy is not without problems or controversy. Conventional plant breeders, traditionally exempted from safety review, were concerned that their new varieties might trigger regulatory scrutiny if the traits were sufficiently “novel” as to attract regulators’ attention. In practice, few non-GE-derived plants considered PNTs have triggered review, and of those that do, the timelines are

abbreviated relative to the procedure for GE-derived PNT plants. Moreover, because much of Canada’s agricultural commodities are exported, these GE crops, not triggering regulation as PNTs in Canada, would still require approvals in importing countries, thus obviating any potential benefit of domestic Canadian nonregulated status. Developers of GE but non-PNT crops in Canada seek CFIA and Health Canada approval as standard procedure to facilitate international marketing. Nevertheless, the scientifically sound foundation of Canada’s PNT policy is increasingly recognized among regulators globally as worth pursuing (ACRE 2013; NRC 2016; Sehnal and Drobnik 2009). Canada’s PNT policy has the added benefit of easily accommodating new technologies, such as NBTs, because regulatory criteria are based on novel features, not on the breeding processes used (Smyth 2017a).

China

China has a unique regulatory system combining both scientifically sound and politically motivated, scientifically unsound elements. In conducting a risk analysis, China requires valid data from assays based on OECD and *Codex Alimentarius* standards. Although these assays are technically solid, the rationale for conducting them is not. That is, like most countries, China triggers regulatory oversight based on a process of GE rather than on the features of the resulting product. In addition, China requires that certain studies and assays be conducted in China by Chinese scientists, in essence duplicating work conducted elsewhere. China also refuses to even consider an application for approval of a GE cultivar until the producing country has fully approved the same event. This stipulation necessarily introduces delays in the approval process because a plant containing a new GE event can be fully approved and in production by farmers in an originating country (and perhaps end up in shipments to China) prior to Chinese regulatory approval.

Other Countries: Cartagena Protocol

Many other countries are signatories

to the Cartagena Protocol (CP) and have formulated their biotech regulatory policies using the CP framework. The CP is a subsidiary agreement to the Convention on Biological Diversity and purports “... to protect biological diversity from the potential risks posed by living modified organisms resulting from modern biotechnology” (CBD 2000). Curiously, of all the human activities that have damaged biodiversity, the only one singled out for regulation and control is GE, a technology that, in contrast to some unverified claims, has never been shown to damage biodiversity.

The CP refers to viable GMOs as “living modified organisms” (LMOs), and “modern biotechnology” means that a plant has had a nucleic acid injected into it, a definition that captures a broad spectrum of modified plants. The CP regulates LMOs, excluding those meant for medical purposes (transferred across international borders), and mandates that member countries have procedures in place for environmental risk assessment of LMOs, “taking also into account the risks to human health.” The CP is based on the premise that a GE organism is categorically riskier than its non-GE counterpart and that extraordinary measures are thus needed to protect biodiversity from the hazardous effects of GE crops.

The CP was finalized and adopted in the absence of scientific experts, and their absence is apparent from the fundamental flaw of assuming that biological diversity is particularly threatened by living products of biotechnology when there is no scientific evidence to support such an assumption. Nevertheless, 171 countries are signatories (conspicuously absent are major grain exporting nations [e.g., the United States, Canada, and Argentina]). As a result, biotechnology regulations in the ratifying countries are heavily skewed in deference to various interpretations of the precautionary principle/approach, which is often misinterpreted and misapplied.

The CP has become a morass of ideologically based requirements in which compliance is virtually impossible (Smyth 2017b). As such, the CP has done more to delay the international deployment of GE crops than any other factor, thus foregoing benefits of the technology,

⁴ Cisgenics (aka “intergenics”) refers to DNA recombination from the “same species,” in contrast to “transgenics,” in which DNA segments from different species are recombined.

including yield gains, which in turn would protect biodiversity by mitigating the need for the conversion of wildlands to farmland to maintain harvest goals.

Clearly, regulatory barriers deny benefits to farmers and society, not only in the United States but around the world, and do so without any scientific evidence that GE crops are any less safe than crops from conventional breeding methods.

Additional Barriers to International Trade

Even after acquiring U.S. regulatory approvals of a GE crop, the developer can still face uncertainty associated with the regulatory system that carries political risk and potential economic liability. One example is the adventitious presence/LLP (low-level presence) issue (discussed later). Also, the diversity of regulatory authorizations needed has been a major factor in impeding the research and development of GE-derived traits. The costly and onerous regulatory approvals required for GE crops, combined with the lack of harmonization of regulations around the world has effectively blocked the utilization of many beneficial traits. As understated by Graff, Zilberman, and Bennett (2009), “The potential welfare-enhancing nature of some of these undeveloped traits warns of potential social costs from foregone innovation.” This problem will worsen now that the EU has decentralized such approval to individual member states rather than through a common regulatory system (Lynas 2015). Compounding this are the differential conditions for regulatory approval in different jurisdictions. For example, the crossbred progeny of two approved GE events is not regulated further by U.S. agencies, but it is in the EU, even if both parents are approved there.

Hallerman and Grabau (2016) document a number of additional barriers to global approval and adoption of GE crops, including regulatory and public acceptance issues, validating a number of case studies in which GE crops could have improved food security and sustainability.

International Trade Disruptions due to ‘Zero Tolerance’ for GE Products

In today’s globalized and commoditized agriculture, maintaining separate production streams for GE products without any commingling is an impossible task. Therefore, the most pernicious and common obstacle to trade is the invocation of the “zero tolerance” standard, in which the mere detection of an unknown or unapproved GE material in a shipment results in a rejection of the entire shipment. Because a certain amount of adventitious presence due to either commingling or crossing is virtually inevitable (CAST 2006), the consequent LLP of “unwanted” material is also inevitable.

Trade disruptions triggered by unapproved GE material detected in shipments fall into two general categories: asymmetric approvals and asynchronous approvals.

The former (asymmetric) can occur with GE crops intended exclusively for domestic use, such as certain virus-resistant squash varieties (Seminis 2017) that are produced and consumed within the United States, so there is no (apparent) need for foreign approvals. Because of “zero tolerance” policies and the sensitivity of molecular detection assays, however, even minuscule amounts of GE material mistakenly sent to foreign markets can result in a trade disruption (see later). To minimize chances that the squash will end up in international commerce, producers may only sell for the fresh market for immediate domestic consumption. This asymmetric approval approach might work for individual unit products, such as squash or watermelon, but it is impracticable for commodity grains, which include the majority of GE crops. Even so, the risk remains that the produce might end up in international resorts, cruise ships, or other venues where they are not permitted. Such liability may be decreased by restricting production to selected growers under contract, rather than to producers at large, but not all crops are suited to such a production model, and even this cannot guarantee zero presence in shipments.

To date, most trade disruptions involve “asynchronous approvals,” in which an

internationally traded GE crop is approved and cultivated in one country prior to approval in a recipient country. These trade problems are more fully analyzed in CAST (2016).

Trade disruptions due to LLP of GE content are well documented, with several high-profile incidents and a number of less well-documented cases occurring since 2006, GE Herculex corn and GE flax in 2009 being prominent examples (CAST 2016). Every disruption based on detection of an unapproved GE product to date has been due to LLP in which the detected quantity of unapproved GE material was less than 1%.

Shipments of U.S. soybeans were quarantined in EU ports in 2009, not because the GE soy was unapproved, but because of the detection of residual dust from a prior shipment of GE corn (USDA–FAS 2010; Wager and McHughen 2010). In 2013–2014, China refused shipments of U.S. corn because of their detection of trace amounts of Syngenta’s Mir162 variety, which had been approved in the United States but was awaiting Chinese approval (USDA–FAS 2014). In a recent court settlement, Syngenta has agreed to pay \$1.4 billion in damages from this case.

Another example is the Liberty Link rice (LLRice) “adventitious presence” incident in 2006 (Lemaux 2007) that resulted in a \$750 million settlement against Bayer Crop Sciences in one case alone, with the total litigation payout of more than \$1 billion. For LLRice, USDA–APHIS quickly determined that the inadvertent presence of the genetic insertion “present[s] no human health, food safety or environmental concerns. The protein found in Liberty Link rice is also approved for use in other products and has been scientifically reviewed and approved for use in a dozen countries around the world” (USDA–APHIS 2007). Thus, the very fact that there is a regulatory scheme for harmless products (USDA–APHIS has yet to deny any valid deregulation petition) that brings with it a risk of potential liability and huge economic losses solely because such products are regulated certainly discourages academic (and philanthropic) institutions and small businesses from participating.

These international trade issues create

unique hurdles for vegetable breeding/seed companies, many of which market seeds in more than 100 countries. The logistical and legal challenges of meeting each country's regulatory requirements are virtually insurmountable, leading such companies to avoid use of rDNA technology. Even getting to the point of having seed to sell in a receptive market would be a Herculean task, because a given variety of a single species may have passed through five or more countries around the world for off-season backcrossing or generation advancement, parent line production, hybridization, processing and packaging, etc. Just obtaining the permits for entry and exit of the seeds from such small production lots, even when done in greenhouses, is an administrative burden and carries potential liability. Thus, even if a company has a large market in a single country where specific GE varieties might be grown and the products channeled to appropriate markets, breeding and seed production of those varieties often would need to occur at multiple international locations. The threat would also require complete isolation of GE and non-GE breeding and seed production locations and infrastructures. The lack of common international regulations for GE crops is likely to remain a virtual veto on developing GE products for vegetable and other specialty crops.

Whether asymmetrical or asynchronous, trade disruptions are especially costly when shipments are rejected because of the LLP of safe but unapproved GE products in a particular market (CAST 2016; Kalaitzandonakes et al. 2016; McHughen 2016; Stein and Rodríguez-Cerezo 2010). A Panamax ship full of grain rejected at a destination port because of the detected presence of a GE product unapproved in that port's jurisdiction sets off a serious and expensive set of reactions. In such trade disruptions, no one "wins"; the exporters lose a sale, the importers lose a shipload of grain, the farmers lose markets, animals end up hungry, and the consumers end up paying more, without any corresponding increase in safety. Such trade disruptions are especially frustrating when the unapproved GE detection is unverified or at de minimis levels (at or below a level of technical detection) and therefore also far

below the amount that might cause harm (CAST 2016).

Harmonization of Standards for LLP Thresholds to Eliminate Trade Disputes

The WTO was established partly to address and obviate trade disruptions, with an explicit prohibition against rejection of goods in the absence of scientifically documented hazards. Unfortunately, the WTO is often ignored as a resolution body in these matters, and otherwise avoidable trade disruptions continue apace. Also unfortunately, the office of the U.S. Trade Representative has not actively challenged trading partners for ignoring agricultural biotechnology-related WTO obligations. The OECD has been active in trying to formulate means to address the zero-tolerance problem and has published a report on its discussions (OECD 2013). Mechanisms to obviate trade disruptions include abbreviated local reviews, based on *Codex Alimentarius* guidance, for which the GE commodity has been approved in the exporting country (Demeke and Perry 2014). Alternatively, countries could adopt a nonzero tolerance for LLP of asynchronous GE crop events for which approval is sought but not yet approved in the receiving country. Canada and Colombia are considering adopting such a nonzero tolerance for asynchronously approved GE crop commodities (Tranberg and Lukie 2016). Another option is to simply recognize the safety findings and approvals conducted by appropriate trading partners (Demeke and Perry 2014). Vietnam has recently legislated such recognition to obviate trade disruptions due to asynchronous approvals (Gruère 2016). Finally, the exporting countries might invoke current WTO rules requiring importers to accept shipments, unless the importers provide scientific evidence of hazard to justify refusing a shipment (WTO 2008).

As more GE crops are developed and cultivated worldwide, the number of trade disruptions will only increase without a common LLP policy to circumvent these inevitable and expensive trade disruptions. The problem will be exacerbated with virtually undetectable gene-edited products entering international

trade, especially those that are deemed unregulated in the exporting country but regulated in the importing country (Kahrman, Börneke, and Leggewie 2017; Wager and McHughen 2010). Until international markets are held to their WTO obligations, small companies and public institutions, especially, cannot afford to risk the liabilities.

AGRICULTURAL BIOTECHNOLOGY INNOVATIONS IN ACADEMIC INSTITUTIONS AND SMALL BUSINESSES

In the early 2000s, funding agencies, particularly the USDA Small Business Innovation Research program directors and colleagues, recognized that their investments in small company development of genetically engineered crops were not translating to commercial products. Similarly, since the early 1980s, public sector (especially the USDA) and academic breeders had been well funded from (mainly) taxpayer sources to research and develop agricultural biotechnology to breed improved crops. But successful examples, as noted earlier, are sparse. Regulatory requirements were recognized as the major barrier, and thus a workshop to address this issue was held in 2004. The Specialty Crop Regulatory Initiative (SCRI) arose from that workshop and organized the second meeting in 2005. The SCRI deliberations fleshed out the questions and the scope of the problem, i.e., the number of potential improved crop plants that were shelved for lack of a path to regulatory approvals.

These discussions led to the first Specialty Crop Regulatory Assistance (SCRA) workshop in 2011, which brought GE crop developers from academic and small and medium-sized enterprises (SMEs) together with the federal regulators. Other attendees included regulatory consultants and other GE crop developers. Three case studies illustrated the role of the regulatory agencies in evaluating GE crops: plum pox-resistant HoneySweet™ plum developed by USDA-ARS, *Sclerotinia* blight-resistant Blight Blocker peanut, and insect-resistant Spunta-G2 Bt-potatoes. In each case, the developer presented the

laboratory work involved in developing the crop, including the gene construct and the method of gene introduction. The regulatory agencies commented on their processes and the specific crop, and they offered avenues of assistance and contacts. A workshop report is posted on the SCRA website (SCRA n.d.).

This SCRA workshop was repeated in September 2016, with case studies of citrus trees resistant to citrus greening (Huanglongbing) via the incorporation of defensins, which is under development by Southern Gardens. A second case study described a Simplot W8 potato that lowers browning, asparagine, and reducing sugars as well as incorporates resistance to potato late blight. The third case study presented a cotton variety with ultralow gossypol levels so that the seed could be used as a feed protein source.

Although these workshops addressed the regulatory barriers faced by SMEs and academics, some 300 traits in approximately 80 crops have been shelved, with the projects terminated or dormant, remaining to be activated and commercialized (Miller and Bradford 2010; Ricroch and Hérnard-Damave 2016). The intent of the SCRA is to encourage and facilitate commercialization of these important innovations for farmers, the public, and the economy. In spite of these activities, the cost of collecting data for regulatory dossiers that do not directly inform safety is still a substantial barrier and can only be lessened by a revised regulatory structure.

Those few products developed in public or smaller private entities that did successfully navigate the U.S. regulatory system faced some additional obstacles not encountered by the major GE crops. The companies breeding GE cultivars of (mainly) large annual field crops have employee groups dedicated exclusively to regulatory approvals and a well-established regulatory pathway based on approvals going back to the mid-1990s. In contrast, public, academic, and small private breeding establishments often develop improved GE cultivars of small market crops, including small acreage field crops and horticultural, perennial, and tree species. These species do not fit neatly into the template established for major field crops, so regulators are less

comfortable in processing the dossiers and ask for additional data. The requirements for data can be acute when regulators do not distinguish between “nice to know” and “need to know” information. Academic institutions and smaller companies usually do not have the capital to acquire unnecessary data and have to abandon projects.

Similarly, regulatory compliance costs are often well beyond the value of a smaller crop so costs can never be recouped, even with a highly successful product. Bigger companies can decide to simply spend the money to acquire requested data, particularly if it expedites approval of their product, then factor those costs into the ultimate pricing of the commercial product. Providing such data, however, leads to increased data expectations that the next dossier may be expected to meet. After 20 years of providing increasingly unnecessary data, the bar has been set almost impossibly high for all but the largest GE crop developers.

Regulatory Burdens, Precommercialization

Regulatory oversight of agricultural biotechnology innovations begins in the research laboratory, and it can be particularly intensive if the intent is to commercialize the final product for food and feed. Entire categories of genes are avoided because they are unlikely to be approved, and they include genes for glycosylated proteins, proteins resistant to digestion, proteins from allergenic motifs, or proteins from vertebrates or other animals.

Whether intended for commercialization or not, rDNA activity in academic laboratories requires a biological use authorization from an institutional authority. The protocols and specific methods to be used, vectors, sequences, etc., must be specified and approved. Safety protocols based on risk level are specified in these authorizations. If transgenic plants from other researchers are to be used, and seeds or propagules of those plants are to be sent across state lines or tested in a field, a notification or permit is required from USDA-APHIS that also mandates comprehensive information about the modifications and design protocols to

mitigate probability of persistence in the environment.

Research on regulated GE crops faces several additional requirements not mandated on research with nonregulated plants. These include growing the biologicals under contained environments unless field release permits are obtained. To ensure identity preservation, design protocols included in the permit application must specify labeling designations, transportation methods used, plot designs, and devitalization procedures of the regulated items. In addition, the design protocol needs to document post-harvest scouting procedures to monitor for volunteers (Van Deynze et al. 2016). These restrictions put significant burdens on public institutions and small businesses because they remove experimental land from normal crop research use during the quarantine period, which ultimately drives research costs up.

Research on regulated perennial crops poses additional challenges, because the containment and quarantine extends to fruit, prunings, etc., which must be identity preserved and devitalized. For example, the public sector developers of the virus-resistant plum technology were required to maintain such identity preservation protocols in orchards for 15 years while the variety was making its way through field testing, including 8 years in the regulatory system before it was approved by USDA-ARS in 2011 (Scorza et al. 2013).

Numerous other potentially valuable traits for perennial crops have failed to progress into production because of the logistics and expense of such requirements well before the formal regulatory or commercialization phase (Driver, Castillon, and Dandekar 2004). In another example, the private philanthropic organization 2 Blades Foundation (2 Blades Foundation 2017) supported research with several universities to transfer bacterial spot resistance from pepper to tomato. Pepper and tomato are closely related, and the resistance gene is present (and therefore consumed already) in commercial peppers. The pepper gene functioned in tomato as predicted, and it holds great potential to mitigate use of toxic copper-containing bactericides currently used in disease-management

practices by the Florida tomato industry (Horvath et al. 2012).

This and similar traits, however, have not advanced toward deregulation because of compliance costs and indifference from the tomato industry for marketing a GE product (McDivitt 2017). These regulatory compliance costs might be justified if there were safety issues to address, but there are none. In contrast, mutagenized plant populations, which can have extensive genomic disruptions (Li et al. 2017), require no special conditions, notifications, or permits to be cultivated and consumed. Mutagenized crops (like GE crops) have never caused verified harms.

Finally, in addition to the regulatory compliance costs per se, the pending imposition of mandatory marketing disclosure of GE products in 2018 (see later) also presents significant hurdles for academic and small business breeders, particularly for specialty crops.

Regulatory Compliance, Deregulation

As noted earlier, there are few cases in which universities and small businesses have obtained regulatory approval for GE products (e.g., Bennett et al. 2013). The case of the ringspot virus-resistant papaya developed at Cornell University is unique, but it was also developed very early in the history of GE regulation, as was the transgenic soil remediation Triffid flax from the University of Saskatchewan (Fuchs and Gonsalves 2007; Gonsalves 1998; McHughen et al. 1997). Today, approval processes for these crops would be much more elaborate.

More recently, a small company (Okanangan Specialty Fruits Inc.) successfully moved three nonbrowning apple varieties through the regulatory process (Carter 2012) and J. R. Simplot Company has deregulated several varieties of Innate® potatoes (USFDA 2015). In the former case, the company persisted for five years under regulatory review, an especially difficult process for a small company to support. As has been documented previously (Bradford, Alston, and Kalaitzandonakes 2006; Kalaitzandonakes, Alston, and Bradford 2007; Miller and Bradford 2010), the challenges for

breeders of GE specialty crops to successfully navigate the expensive and time-consuming regulatory processes are, at best, daunting.

In addition to the regulatory process itself, university intellectual property and technology transfer offices are hesitant to take the administrative burdens and legal risks of entering the regulatory approval process. After spending resources on patenting discoveries and innovations underlying GE-derived technologies, there is little appetite to assume the further expenses associated with deregulation. At this point, public institutions may seek a commercial partner to assume all or part of the risk and expense. Given the difficulty of conducting extensive trials on GE events, the products often require further development and testing to be attractive for private investment. More often, they end up in the well-known “Valley of Death” between innovation and commercialization in plant biotechnology (Dorey 2009; Graff, Zilberman, and Bennett 2009; Mugge 2015).

A further risk due to the regulatory process has recently been illustrated by the case of the orange petunias (Serrick 2017). In 1987, gene transfer from corn into petunia (Meyer et al. 1987) resulted in novel orange-colored flowers. Although this petunia event carrying the novel transgenic allele was not deregulated, the regulated petunias were unknowingly used in diverse breeding programs, and varieties derived from this “regulated article” have been marketed for years. The wide distribution of this unapproved petunia has now been discovered, and USDA–APHIS felt compelled to seek “voluntary” withdrawal from the market and destruction of any plants and seeds, causing considerable disruption in the ornamental petunia seed industry. This would seem to be an example of a “victimless crime,” in which “laws produce secondary crime, and . . . create new ‘criminals’ many of whom are otherwise law-abiding citizens” (Schur and Bedau 1974), caused by the existence of an unnecessary regulatory regime.

Regulatory Considerations, Postcommercialization

Once a GE event receives regulatory

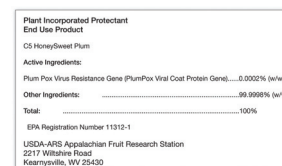
approval in its country of origin, additional obstacles remain, even for domestic markets. Some of these obstacles are regulatory, whereas others are not. Regardless, the barriers all stem from unnecessarily restrictive nonscience-based regulations.

Stewardship

Environmental Protection Agency-mandated stewardship programs are typically imposed on PIP-containing crops. Given the few approved products from universities and small businesses, postcommercialization stewardship has not yet been a major issue. The X17 late-blight-resistant potato developed by Simplot has a mandatory integrated pest management stewardship program and required monitoring of both the efficacy of the gene and documenting reductions in fungicide use. Cases of unexpected damage must be investigated and reported, and records of the seed sold to growers must be maintained.

EPA Labeling

Genes engineered into crops for pest control are classified as PIPs and are equivalent to more traditional pesticides. Like all synthetic pesticides, PIPs must have warning labels. For commodity crops, pesticide labels on seed bags have not been a major inconvenience, particularly since seeds are usually coated with other pesticides anyway. The issue is more problematic for fruits and vegetables. For example, the proposed pesticide label for the virus-resistant Honey Sweet plum (USEPA 2010) led to a refusal of nurseries to carry the GE trees. In addition to using labels, the nurseries also objected to having to be registered as pesticide-producing facilities (Conko et al. 2016). Seed tubers of Simplot’s X17 potato must carry a warning to “keep out of reach of children.”



Non-GMO Labeling

The GE product provider needs to find a grocery retailer



willing to stock it. For many consumers, the term GMO is now associated with “products that should be avoided,” making the unregulated non-GMO label the fastest growing sector of the food market. The Non-GMO Project lists more than 43,000 products that it has certified as GMO free, ranging from foods that could have GE-derived ingredients, such as cereals, to products in which no GE counterpart exists, such as nuts, or is ludicrously impossible, such as salt. The non-GMO market is forecast to grow at more than 16% per year for the next four years (Infiniti Research Limited 2017).

GMO Labeling

The flip side of labeling products as non-GMO is an explicit GE label. Vermont became the first U.S. state to pass a labeling law for GE foods (Act 120), with several other states preparing to follow suit. Faced with the prospect of 50 different labeling laws, the agri-food industry supported the passage of the National Bioengineered Food Disclosure Standard of 2016 (National Bioengineered Food Disclosure Standard 2016) (amending the Agricultural Marketing Act of 1946 S. 764–114th Congress). The specific labeling requirements are still being developed by the USDA’s Agricultural Marketing Service (AMS), but the definition of a GE product to be used for labeling is confusingly different than the definition used for regulation. The law exempts modifications (such as through certain applications of gene editing) that could have been achieved through conventional breeding methods, though it is not clear how that determination might be made.

Regardless, this bill will have post-commercialization implications for all developers of GE crops and will have a disproportionate hardship on universities and small businesses attempting to develop GE crops. Labeling is not just a simple matter of putting a label on a can or box. Labels must be truthful, meaning the supply stream must be segregated and monitored for GE presence (CAST 2014). In addition, mandatory labels must be verifiable, and the cost associated with verification can add considerably to the cost of the food as paid by the consumer (Kalaitzandonakes et al. 2016; McHughen 2000).

The National Bioengineered Food Disclosure Standard also authorizes the use of a non-GMO label. It remains to be seen how consumers will react to these labels, but the GE label could well lead consumers to make false inferences on the safety (or lack thereof) of labeled products (Bar-Gill, Schakade, and Sunstein 2017). Advertising campaigns will likely seize the opportunity to demonize competitors’ products. With current opinion highly polarized on this issue (only 37% of the general public consider GE foods to be safe, compared to 88% of scientists [Funk and Rainie 2015]), labeling policies will certainly influence decisions for bringing new innovations to market.

Until the USDA–AMS releases the details of how labeling will work, grocery manufacturers may find it expedient to simply replace GE ingredients in their products. Then their suppliers inherit the task of ensuring that their products are GE free. Altogether, these considerations—all stemming from purported safety regulations—add unnecessary cost and make GE a difficult “sell” to the entire food chain.

The National Bioengineered Food Disclosure Standard will ensure a uniform national labeling standard for the U.S. market. Passage of this bill, however, is prompting other countries to consider their own labeling requirements. As of this writing, Korea and Japan, among others, are considering new labeling legislation. The food industry obtained its uniform labeling standard for the United States, but at the prospect of a costly patchwork of international labeling standards.

Certification



Products certified as sustainable, fair trade, or other vague but appealing features are becoming increasingly common. Such certifications usually reflect ideology rather than scientific criteria and thus unfairly demonize GE products that, paradoxically, may be more “sustainable” than non-GE counterparts (NRC 2010).

The first major exclusion was in 2000, when organic certification explicitly excluded the intentional use of GE. Two groups particularly important for tropi-

cal products such as coffee and cacao are Fair Trade and the Rainforest Alliance. According to Fair Trade USA (2013), “For Fair Trade Certified products, the most toxic chemicals are not used and there are no GMOs.”

The Rainforest Alliance also certifies farms and follows the Sustainable Agriculture Network standard (SAN 2017), so GE (including NBT) crops are prohibited on the farm premises (Rainforest Alliance 2016).



The problem is especially acute with forestry products, because there is a very limited market for uncertified products.

The Forest Stewardship Council standard, without explanation, states “Genetically Modified Organisms (GMOs) are not used for any purpose (Indicator

6.8.d within Criterion 6.8 of Principle 6)” and lists wood from forests in which genetically modified trees are planted as an unacceptable source (FSC 2017). The other major certifier of forestry projects has similar standards but goes further by prohibiting research. The Programme for Endorsement of Forest Certification stipulates that “[g]enetically-modified (GMO) trees shall not be used” as part of its criterion for “[m]aintenance, conservation and appropriate enhancement of biological diversity in forest ecosystems.” Thus far, only one GE tree—a low-lignin eucalyptus produced by FuturaGene in Brazil—was authorized for commercialization in 2015, but, not being certifiable as sustainable, the tree has no customers.



Transportation

Once a product has regulatory approvals and has arranged retail outlets, conveying the product to market may present issues. If the GE product is approved in its country of origin, all countries of transit, and the countries of market destinations, there may be no problem. Under the United Nations Recommendations on the Transport of Dangerous Goods, also known as the “UN Model Regulations” or the “Orange Book” of 2005, however, the GE product is a Class 9 “Dangerous



Good” subject to restrictions. Except for tiny quantities, it must meet the packaging instruction 959 and be labeled as “UN3245” (IATA 2010).

Regulatory Compliance as a Barrier to Small Companies/Academics

As mentioned earlier, barriers to the development of new GE crops are numerous, including time and cost of laboratory and field trials necessary to generate the dossiers for submission to regulatory agencies. The complexity of the regulatory process is especially daunting to navigate for small-scale businesses or academics. Even if the data could be collected to present a dossier to the regulatory agencies, the years of waiting for decisions and requests for additional data make the task even more costly. The most egregious example of this delay, albeit not a crop, is the GE fast-growing Atlantic salmon, which was in regulatory limbo—with approval held up in regulatory agencies and the White House—for almost 30 years before being finally approved (Van Eenennaam and Muir 2011).

Academics or small businesses should not be exempt from or get a “pass” to circumvent true safety-based risk assessment. But it is clear that many of the regulatory requirements are not scientifically justified to answer any legitimate safety questions. Merely because some companies are willing to pay the price to compile unnecessary data should not set that same high bar for everyone. As stated by the NRC in their 2016 report (NRC 2016 [p. 312]): “One of the predominant concerns raised about the costs associated with regulatory approval of new GE crops and foods is that they may operate as a barrier to innovation in GE crops” (Bayer, Norton, and Falck-Zepeda 2010; Graff, Zilberman, and Bennett 2010; Kalaitzandonakes, Alston, and Bradford 2007; McDougall 2011). “The costs of obtaining regulatory product approval for new GE products may operate as a barrier to entry particularly for public-sector and small private firms” (Falck-Zepeda et al. 2012; Smyth, Phillips, and Castle 2014).

OPTIONS TO FACILITATE REGULATORY APPROVALS WITHOUT COMPROMISING SAFETY

Regulations are designed to assure reasonable safety. Science-based regulations provide that assurance of safety to almost everything, from light bulbs to truck tires.

The best regulations—those that build public confidence because of the successful track record of identifying and mitigating risks—follow the maxim “Regulate commensurate with degree of documented risk posed.” In other words, the most hazardous products receive the most stringent regulatory oversight, whereas the more benign products receive correspondingly less. This sensible, effective maxim has been discarded in regulating agricultural biotechnology, because the massive amount of regulatory scrutiny is grossly disproportionate to the documented risks posed (viz. the same kinds of risks as posed by products of traditional breeding [e.g., NRC 2016; NRC/IOM 2004]).

The U.S. regulatory system as practiced since the late 1980s can claim a notable achievement in that no GE product approved by the regulatory agencies has ever been recalled because of safety problems. Such a claim is akin to putting a fence around Central Park and later claiming the absence of alligators in the park was attributable to the fence. The reason no safety problems were identified by the regulatory process, and why no approved GE products have had to be recalled for safety reasons, is that rDNA is not inherently hazardous (NRC 1987), and therefore regulatory oversight based solely on the use of GE methods is unnecessary.

Focusing limited regulatory resources on relatively benign GE products leaves the public and the environment at greater risk from potentially more hazardous but under-regulated products. The disproportionate diversion of scant resources jeopardizes public trust in the regulatory system.

Crucially, the U.S. regulatory system fails to calculate the “forgone benefits,” the missing number of potentially ben-

eficial GE products that were developed but never commercialized because the developers could not afford the unnecessary regulatory compliance costs (Graff, Zilberman, and Bennett 2010; Wesseler et al. 2017).

How to Regulate Based on Relative Risk without Capturing ‘Traditional’ Breeding

Invoking and applying the regulatory maxim of giving equal scrutiny to products of equal risk encounters a practical problem. With risks being more or less equal (NRC/IOM 2004), it is necessary to give equal scrutiny to both GE and traditional breeding. Thus, either cease regulating GE entirely, or start regulating traditional breeding. But there is no political desire (as well as no scientific need) to regulate “traditionally bred” products. The solution is to shift away from a process-based trigger to a scientifically sound, tiered, “product-risk” trigger



Figure 1. Photo/histogram of files required for regulatory approval of new cultivars.

The stack on the left is the dossier of data files supporting regulatory approval of a GE flax cultivar, which was commercialized but withdrawn based on objections from the EU. The data file on the right is required for a cultivar developed using somaclonal variation, in which spontaneous genetic changes to cells growing in vitro were regenerated into a fertile plant with beneficial agronomic properties. The genetic changes were never characterized, and the plants were never safety tested, but the cultivar became popular with farmers and was grown on millions of acres and shipped around the world, with no regulatory approval anywhere. (Photo courtesy of Alan McHughen.)

(Conko et al. 2016; NRC/IOM 2004).

There is no rational reason why a new crop variety developed using, for example, ionizing radiation, with all of the genomic disruptions that is known to cause, should receive zero regulatory safety oversight whereas a simple gene modification using *Agrobacterium* requires a regulatory review costing millions of dollars. It is unreasonable that current regulatory review is “all or nothing” in that two products posing similar risk should receive such vastly different safety oversight (see Figure 1 for GE and non-GE dossier comparison). There is no mechanism for regulatory scrutiny commensurate with degree of risk posed. If anything, the mutagenic treatment would appear to carry the greater risk, at least superficially, because of the multitude of random unknown genomic changes wrought by mutagenesis (NRC/IOM 2004). Yet 2,700 crop varieties developed using ionizing radiation have been released and widely grown without any safety regulation or safety issues after release (Shu 2009).

If the low (but not zero) risk associated with traditional breeding serves as the benchmark for a regulatory trigger, then only products with a documented risk above that threshold should require regulatory safety assessment (Conko et al. 2016). Using the safety risk of traditionally bred products (or something that could be produced using conventional breeding methods, including mutagenesis and other accepted technologies) as the threshold for regulatory capture provides a scientifically sound basis for a regulatory safety. “Products” here refers to the crop type plus the phenotype of the novel trait (NRC/IOM 2004).

Once designated for regulatory scrutiny, the intensity of scrutiny in a scientific risk assessment is tiered, with each tier commensurate with the degree of identified risk posed (Conko et al. 2016). In other words, on the basis of a preliminary screen, products deemed of low (but above threshold) risk will receive just enough scrutiny to reach a reasonable conclusion on the product safety or need for risk management. Products deemed of higher risk receive proportionately greater scrutiny to reach a reasonable conclusion on the safety of the product.

This “regulate commensurate with degree of risk posed” maxim conforms to the NRC (2016) report endorsing a “tiered” approach to premarket regulatory assessment. It would also give clear signals to potential crop developers, including in academia and small companies, about the types of methods and traits that would meet scientifically sound regulatory requirements and therefore would be economically viable to pursue.

CONCLUSION: THE CURRENT PROCESS-BASED U.S. BIOTECHNOLOGY REGULATORY SYSTEM IS A SCIENTIFICALLY UNJUSTIFIED BARRIER TO AGRICULTURAL INNOVATION

Since the early 1980s, American taxpayers have invested heavily in public (especially USDA and universities) and small private entities to develop improved crops and foods using agricultural biotechnology, including genetic engineering. In spite of this considerable investment, the returns have been scant, with the unnecessarily onerous U.S. regulatory system operated by the USDA, FDA, and EPA largely to blame.

Major multinational corporations have commercialized a handful of GE crops, and these dominate U.S. agriculture, with more than 90% of U.S. farmers choosing to grow GE varieties of corn, soy, and cotton every year. Even for major corporations, however, the ever-increasing regulatory barriers have led to a substantial decrease in the number of petitions for deregulation.

If regulatory compliance is difficult for large companies, small businesses and public institutions have almost no chance to commercialize safe, effective, and innovative GE crops and foods—especially of small market and horticultural crops—so the promising products languish on storage shelves before eventually being discarded. The unnecessarily complicated, onerous, and unscientific regulatory system presents a near insurmountable barrier, which is then compounded by subsequent marketing and labeling is-

ues. Our current system denies potential benefits to farmers, consumers, and the environment, with no corresponding increase in safety, and unduly restricts innovation by public and private sector developers. The current U.S. regulatory system also limits market competition. For example, the cp4 gene conferring herbicide tolerance is off patent. Yet GE crops with a generic cp4 gene are still stymied by the process-driven regulatory landscape, which mandates regulatory review for each new event.

Genetically engineered crops and foods are demonstrably safer than the products they will displace, so the current regulatory barriers perpetuate the continued use of more hazardous, less nutritious, more expensive, and more environmentally damaging crops and foods that face no regulatory scrutiny whatsoever.

Until regulations align with the stated public policy goal of reasonably assuring safety and regulating commensurate with the degree of risk posed—perhaps using the suggestions discussed earlier—public, academic, and small business entities will continue to be frustrated in using these safe tools to deliver useful products to farmers and consumers, and the 35-year history of public and small private investment in agricultural biotechnology will continue to be squandered.

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