

Review Article

US regulatory system for genetically modified [genetically modified organism (GMO), rDNA or transgenic] crop cultivars

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Summary

This paper reviews the history of the federal regulatory oversight of plant agricultural biotechnology in the USA, focusing on the scientific and political forces moulding the continually evolving regulatory structure in place today. Unlike most other jurisdictions, the USA decided to adapt pre-existing legislation to encompass products of biotechnology. In so doing, it established an overarching committee (Office of Science and Technology Policy) to study and distribute various regulatory responsibilities amongst relevant agencies: the Food and Drug Administration, Environmental Protection Agency and US Department of Agriculture. This paper reviews the history and procedures of each agency in the execution of its regulatory duties and investigates the advantages and disadvantages of the US regulatory strategy.

Introduction

Numerous reviews have documented the various regulatory approaches employed by governments around the world to scrutinize the risks associated with products of agricultural biotechnology. Many of these are scientifically sound, comprehensive and well documented, such as those emanating from the US National Academies of Science and other professional scientific organizations. However, they are designed for a technically expert audience or regulatory professionals, and casual interested observers may find them difficult to understand. At the other extreme, a number of non-expert organizations have published reviews claiming that the USA provides little or no regulatory scrutiny of genetically modified organisms [GMOs; also called transgenic or products of recombinant DNA (rDNA) technologies]. Although these are readily readable by non-experts, they contain numerous errors and nonsense. In the middle of the two extremes are various newsletter-type documents designed to give accurate and credible information to non-expert readers; however, these typically focus on one agency or issue, and are insufficient to provide more than a superficial coverage of the field.

Over the last century, agriculture in general and plant breeding in particular have enjoyed vigorous research and the rapid deployment of beneficial developments. Traditional forms of crop genetic improvements, such as selection and cross-pollination, remain the standard tools in the breeder's toolbox, but have been supplemented with a range of new and specialized innovations, such as mutation breeding using ionizing radiation or mutagenic chemicals, wide crosses across species requiring human interventions such as embryo rescue, and gene transfer, commonly called genetic modification or genetic engineering.

In breeding a new crop cultivar, the breeder identifies a genotype with (putative) superior features. The selected genotype is then tested, maintained and nurtured through seed or vegetative propagation until sufficient stock is available for commercial release, presuming the ongoing testing provides satisfactory performance data. In the USA, the commercial release of a new seed or tuber propagated crop cultivar can be a relatively simple procedure, with new variety registration under the authority of the Plant Variety Protection Act 1970/1994 [administered by the Plant Variety Protection Office at the US Department of Agriculture (USDA); see

<http://www.ams.usda.gov/Science/PVPO/PVPindex.htm>]. The breeder, in most cases, generates a population of plants with a uniform, identifiably novel, genetically stable genotype. The genetic variation may be generated by any of the methods outlined above, or the breeder may carefully inspect and select amongst the natural genetic variation within any given population. Subsequent analysis and testing can take several years to ensure that the beneficial features are indeed stable, heritable and expressed adequately over generations, with consideration taken of climatic fluctuations and regional soil types. At the same time, the new genotype is evaluated for agronomic (yield potential, reactions to relevant diseases, etc.) and product quality (e.g. oil profile for oilseeds, starch or flour for grains, etc.) characteristics. Finally, prudence (if not fear of liability and litigation) dictates that responsible breeders evaluate the new genotype for any modulations in the production of anti-nutritional components (for more information on general plant breeding procedures, see McHughen, 2000). Most crops produce undesirable substances, such as allergens or toxicants, and years of breeding has successfully reduced – but not eliminated – these anti-nutritional substances. On rare occasions, new genotypes express elevated levels of toxicants, requiring the rejection of otherwise good performing new cultivars. This selection process eliminates almost all potentially hazardous cultivars before they can be experienced by farmers or consumers; therefore, this phenomenon is largely unknown to ordinary consumers, as is the realization that virtually all foods contain small amounts of naturally occurring toxic substances which are harmless – or at least unobserved – when consumed in modest quantities (see, for example, Ames *et al.*, 1990). On those rare occasions when potentially hazardous cultivars are released commercially, damage is limited by recognition of the problem and removal from the market. Probably the best known example is the Lenape potato, which had to be removed from the market after it was found to generate dangerously high levels of the glycoalkaloid solanine (Akeley *et al.*, 1968; Zitnak and Johnston, 1970).

Other examples of unexpectedly hazardous conventionally bred crops are outlined in US National Academy of Sciences (NAS) (2004a) and Kuiper (2003). Overall, however, the incidence of unexpected or unintentional genetic changes resulting in a hazardous crop – regardless of the method used to create the genetic modification – is extremely low, and there are few documented examples (NAS, 2004a). As a result of this traditional safety record, the USA does not routinely regulate the safety of new crop cultivars, instead relying on breeders and developers to exercise due diligence and prudence in their evaluations, a system that has worked remarkably well considering the lack of hazards reported for

new crop cultivars over the years, and continuing with newer methods of genetic modification as they are deployed to crop improvement. For example, mutation breeding, using ionizing radiation or mutagenic chemicals to randomly disrupt DNA in crop plants, has been used since the mid-20th century, producing over 2200 crop cultivars (Food and Agriculture Organization database), none of which have had the relevant DNA mutations fully characterized, and none of which have had to be removed from the market for safety reasons.

Background/history of the US regulatory framework for plant biotechnology

The historical assumption that changes in plants as a result of genetic modification in breeding are generally safe and benign was eventually challenged with the advent of rDNA technology in the early 1970s. When Cohen and Boyer successfully connected two different pieces of DNA (Cohen *et al.*, 1973) and thus initiated rDNA technology, the scientific community recognized not only the great potential for benefits of this genetic engineering, but also the potential for risk (Berg *et al.*, 1974). As a result, interested and concerned scientists and others met at Asilomar, California, and recommended a cautious evaluation of rDNA technology and the products resulting from the use of rDNA, including genetically engineered organisms (GEOs), sometimes called 'genetically modified organisms' (GMOs) (Berg *et al.*, 1975). Although the Asilomar recommended guidelines were largely suggestions and voluntary, the US National Institutes of Health (NIH) formed an rDNA advisory committee to mandate and establish as compulsory a set of rules regulating rDNA research in federally funded programmes (NIH, 1976; later refined: NIH, 1978). This step was followed by similar compulsory mandates from the USDA, Environmental Protection Agency (EPA) and Food and Drug Administration (FDA), thus effectively making rDNA research tightly regulated across the USA, as virtually all rDNA research was conducted with either funding from or in association with one or more of these agencies.

When it became clear that crops improved using rDNA technologies were on the horizon, serious scientific regulatory analyses were initiated in the USA and elsewhere, even before transgenic plants were first developed. Discussion of the environmental and health risks associated with the application of rDNA technology to plants and crops was largely hypothetical initially. This limitation did not impede the scientific rigour of the investigation of the potential hazards or fuel the demand for onerous regulatory scrutiny. The first major such report was issued by the Organization for Economic Co-operation and Development (OECD) in 1982, just prior to

the first report of transgenic plants. The OECD report was influential for a number of reasons, one being that it standardized a definition of 'biotechnology' ('... the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services'; OECD, 1982). Shortly after, NAS issued a paper on the risk assessment strategies in the USA (NAS, 1983). This was just in time, because, later that year, NIH authorized the first environmental release of a GMO (an ice-minus bacterium, described in Lindow and Panopoulos, 1988), and the first transgenic plants were finally documented. At the 1983 Miami winter conference, and more fully documented in the scientific journals shortly after, Schell and van Montague described transgenic tobacco resistant to methotrexate and kanamycin (Herrera-Estrella *et al.*, 1983; Schell *et al.*, 1983), Fraley, Rogers and Horsch from Monsanto detailed their success at generating transgenic petunia plants resistant to kanamycin (Fraley *et al.*, 1983a,b), and Chilton talked about her team's work on the insertion of kanamycin resistance into tobacco (Barton *et al.*, 1983).

With technical, regulatory and even judicial developments (e.g. court challenges to the approval for environmental tests of the ice-minus bacterium) speeding up as a result of the rapid technological developments and adaptation of technical advances from model species to commercially used species, the White House established a committee at the Office of Science and Technology Policy (OSTP) to recommend a mechanism to regulate the quickly advancing technology. The result was a publication outlining several important points. Most important, the OSTP concluded that rDNA was not inherently risky and that regulations should focus on the risks of products, not the processes used to develop them; therefore, the products of rDNA needed no new or special regulatory attention (OSTP, 1986). Instead, current legislation and regulations designed for current products could be adapted to deal with products of biotechnology. The co-ordinated framework also recognized the concept that GMOs were not inherently riskier than other, non-modified organisms. Finally, the OSTP document assigned regulatory priority amongst the relevant federal agencies: USDA, FDA and EPA (OSTP, 1986).

Under the co-ordinated framework, USDA was to be the lead agency in the evaluation of plants as potential pests of agriculture, FDA was to review GMOs as potential threats to the food and feed supply, and EPA was to take priority in evaluating new GMOs with pesticidal properties. Many or most GMOs were to be reviewed by two or even three agencies, depending on the features. For example, a GMO in which the resulting food or feed was not altered, or an

ornamental crop variety with no intended food or feed use, would not need to be reviewed by the FDA. However, every commercialized GMO plant to date has sought and completed a voluntary FDA consultation, even though the food or feed composition was identical to that of the non-modified comparator cultivars.

In recognizing the similarity of the risks posed by the products of novel biotechnologies with those of earlier technologies, the co-ordinated framework rejected the need to create an entirely new bureaucracy to regulate the new products, as was recommended by some individuals, and instituted in, for example, the European Union (McHughen, 2000). Instead, the USA assigned risk assessment, analysis and management responsibility to those already holding and exercising appropriate expertise in existing agencies. Thus, for example, the regulatory expertise in pesticides within the EPA was tapped to regulate GMOs with pesticidal issues. Not only did this strategy avoid the cost of establishing a new layer of bureaucracy (to house new agencies to regulate GMOs exclusively), it also avoided the dilution of relevant expertise and resources caused by the redistribution of those resources across different departments.

The OSTP regulatory approach was validated by the scientific community in a white paper from NAS in 1987, reinforcing the concept that the hazard resided in the product, not in the process by which it was made, and that rDNA posed no novel risks – the risks were 'the same in kind' as those presented by non-rDNA-generated organisms (NAS, 1987). A follow-up study considered more practical issues relating to a risk framework with the environmental release of genetically modified (GM) microbes and plants (NAS, 1989). Subsequent scientific panels focusing on more and more specific aspects of biotechnology consistently came to the same conclusions: (i) all methods of genetic modification, including traditional breeding, can give rise to potentially hazardous products; (ii) biotechnology is no more likely to result in a hazardous product than traditional methods of breeding; and (iii) the regulatory trigger for risk assessment should be based on the physical features of the product rather than on the process by which the product was generated (NRC, 2000, 2002, 2004a).

US regulatory agencies

US Department of Agriculture

The USDA, through the office of Biotechnology Regulatory Services (BRS) of the Animal and Plant Health Inspection Service (APHIS), is primarily concerned with protecting agriculture and

the environment (broadly interpreted) from potential pests (also broadly interpreted). The USDA regulates all genetically engineered (GE) plants prior to environmental release, including the import, interstate movement, small and large field trials and, of course, commercial (farm) cultivation. Today, the legislative authority arises from the federal Plant Protection Act (PPA) of 2000, which consolidated related responsibilities until then distributed amongst several earlier statutes, including the Plant Quarantine Act, the Federal Plant Pest Act (FPPA) and the Federal Noxious Weed Act. Although the legal definition is complex, in simple practice, the USDA considers a 'regulated article' to be a plant and its progeny arising from a specific transformation event. A corn plant, for example, with a DNA construct carrying a *Bacillus thuringiensis* δ endotoxin (*Bt*) gene inserted would be a 'regulated article' until such time (if ever) the USDA approved a petition for non-regulated status (see below). The USDA justifies regulating each event separately because, it argues that the locus of insertion, which varies from one transformation event to another, even using identical DNA constructs and host plant genotypes, may give rise to different inserted gene expression patterns or gene product levels and, perhaps, affect other features (e.g. via the insertional knockout of endogenous genes). Interestingly, once a 'regulated article' achieves 'non-regulated status', the GE plant can be released commercially with no further USDA regulatory oversight. Two such deregulated GE plants can even be bred together to produce a hybrid combining the novel features of each parent, without invoking additional USDA regulatory oversight.

Field trials with GM plants

The USDA initially authorized field trials under the FPPA of 1957. This statutory authority was later consolidated and updated in the PPA of 2000.

In the 1987 Federal Register, the USDA published the first regulated procedure to allow field trials of GMO plants (see 7 CFR 340). After the initial five applications in late 1987 (three for herbicide-tolerant tomato, two for herbicide-tolerant tobacco; NRC, 2000), field trial applications increased dramatically. In the subsequent few years, the USDA issued 16 field trial permits in 1988, 30 in 1989, 51 in 1990 and 90 in 1999 (<http://www.isb.vt.edu/cfdocs/fieldtests1.cfm>). To date, over 12 000 regulated field trials have been authorized. The GE plants included such species as tomato, tobacco, soybean, cotton, cucumber, poplar, potato, alfalfa, squash, walnut, melon, rice, canola, corn and others. Novel traits being tested included not only various marker genes, but agronomically interesting traits, such as herbicide tolerance, insect protection, delayed ripening and disease resistance.

The full listing of such USDA-administered trials is available at <http://www.isb.vt.edu/cfdocs/fieldtests1.cfm>.

Notifications

The USDA now administers regulations governing GE plants through its BRS office within APHIS. Most field trials are approved under the notification procedure, which is the quickest and easiest process designed for the simplest or most familiar GE plants. Usually, notification involves the submission of a letter to BRS documenting how the proposed GE plant meets six criteria and designated performance/characteristic standards. The criteria include such considerations as the GE plant not being of a noxious weed species, and not transformed with human or animal pathogenic sequences. The notification procedure does not apply to plant-made pharmaceuticals (PMPs) or plant-made industrial products (PMIPs). The notification can be used for field trial approval as well as importation and transport within the USA of specified GE plants (for details on the requirements for the notification procedure, see 7 CFR 340.3).

Permits

A permit applies for those GE plants not meeting the requirements for notification, e.g. if the GE plant species is a noxious weed, or if the GE plant species is benign, but the genetic alteration results in a PMP. In issuing a permit, BRS is primarily concerned with biosafety, i.e. the unintended release and spread of a potential plant pest. The permit procedure is much more elaborate than notification, and requires much more information and data. The regulatory requirements for permits are documented at 3 CFR 340.4, and online information and assistance are available at <http://www.aphis.usda.gov/biotechnology/permits.shtml>. The application itself is available online at <http://www.aphis.usda.gov/brs/pdf/2000.pdf>, and can be submitted online via e-permits (see http://www.aphis.usda.gov/permits/brs_epermits.shtml) or manually with hard copy (see <http://www.aphis.usda.gov/brs/pdf/usersguide.pdf>). A draft revision of the guidance for submissions to BRS is currently under review. This is available at http://www.aphis.usda.gov/brs/pdf/brs_usersguide_4_Doc_Prep.pdf.

In March 2003, in response to concerns surrounding non-food substances in transgenic plants and a series of highly publicized permit violations, APHIS announced that it would strengthen mandatory permit conditions for the field testing of transgenic crops, including field trials for PMPs. The number of site inspections would increase to five during the trial and two in the following season. The permits for pharmaceutical trials with transgenic corn (a common host plant species) imposed several conditions, including that no corn could be

grown within one mile of the trial site, that no food or feed crop could be grown on the site in the following season and the size of the buffer zone was doubled (for more details on the regulatory aspects governing PMPs, see Stewart and Knight, 2005).

Deregulation and commercial release

In 1992, the USDA proposed regulations to remove regulatory oversight of those GE plants deemed (after appropriate investigation) to be environmentally benign. In this proposal, GE plant developers could petition the USDA seeking 'non-regulated status', which would then allow commercial release. The proposal was approved and put into effect in 1993, with the first GE plants achieving non-regulated status in that first year. The initial cultivars were a delayed ripening tomato, later known as Flavr Savr™, from Calgene, a viral disease-resistant squash from Upjohn, a bromoxynil-tolerant cotton from Calgene, and a glyphosate-tolerant soybean from Monsanto. To the end of 2006, over 100 GE plants had achieved non-regulated status via the petition process; all of these are documented at <http://www.isb.vt.edu/cfdocs/biopenitions3.cfm>. An example of a petition for non-regulated status for a GE plant under 7 CFR 340 is given at <http://www.agbios.com/docroot/decdocs/04-225-005.pdf>. The APHIS responses, including the 'Environmental Assessment' (EA), 'Finding of No Significant Impact' (FONSI) and 'determination of non-regulated status', are available at http://www.aphis.usda.gov/brs/aphisdocs2/98_33501p_com.pdf.

During the process of considering the petition, the USDA prepares at least two documents – an EA and 'determination of non-regulated status' – to satisfy environmental safety issues under FPPA and the National Environmental Policy Act (NEPA), the latter because, according to NEPA, the USDA must perform an EA if the GM plant shows the potential for 'a significant environmental impact'.

National Environmental Policy Act

The NEPA of 1970 requires most federal agencies to investigate environmental impacts prior to making certain decisions or taking certain actions that could pose environmental risks. The relevant agency starts by asking: 'Is this decision or action likely to have significant environmental effects?'. It then pursues an answer. The simplest is a 'categorical exclusion', which includes items or actions with properties determined by the agency, based on their experience and familiarity, to pose insignificant effect on the environment. After ascertaining that no extraordinary circumstances exist (caused by, for example, unique regional features or endangered species), the agency can approve the application. If the proposal does

not warrant a categorical exclusion, or if it may present significant environmental effects, the agency conducts and publishes an EA.

The EA is a critical analysis of the environmental consequences of conducting the proposed activity or releasing the item. After reviewing the varied relevant factors, the agency can conclude that the proposed activity/item demands additional analyses [and issues a 'Notice of Intent' (NOI) to prepare a more elaborate 'Environmental Impact Statement' (EIS)], or that the proposed activity/item poses insignificant risk, and prepares another document, the FONSI. The FONSI summarizes the EA (or otherwise appended) and justifies and provides a rationale, using the data presented in the EA, as to why the agency came to the conclusion that the item/activity was deemed to be environmentally benign. Both the EA and the FONSI are public documents, and the public has various opportunities to comment and provide input to them.

If the EA suggests that the proposed activity or item might present a significant environmental impact, the agency can publish the NOI in the Federal Register. The NOI includes information on the proposed action/item, outlines how the agency plans to proceed with an EIS and how the public can contribute, and provides contact information at the agency. The plan, also called the 'scoping process', identifies specific relevant issues for in-depth investigation and a time line for completion.

The EIS is a major analysis document, requiring careful deliberation and active wide consultation. When the agency completes a draft EIS, a 'Notice of Availability' (NOA) is published in the Federal Register, which opens the draft to public comment. For at least 45 days, anyone can read and provide input to the agency, which may additionally provide other forums (such as public meetings) to solicit broad public input. The agency is required to take public comments seriously and to respond to all reasonable such input in preparing the final EIS. When the final EIS is completed, the agency publishes another NOA in the Federal Register, which signals another 30-day (or more) waiting period before a final decision is made.

Eventually, the agency publishes a 'Record of Decision' (RoD), the final step in the whole process. The RoD summarizes and discusses the issues investigated in the proposed activity/item prior to making the final decision. The RoD is publicly available, but not necessarily published in the Federal Register.

The foregoing is a quick review of the NEPA involvement and procedures, but necessarily omits various exceptions, exemptions and appeals procedures. A comprehensive description is given on the NEPA website (www.nepa.gov) or in one of the many books on the subject.

Current status

Not everyone agrees that the USDA properly follows its own operating procedures. Three recent federal district court suits challenged the USDA for improperly regulating GE plants. Two suits related to field trials (GE herbicide-tolerant turfgrass in Oregon; pharmaceutical-producing corn and sugar in Hawaii) and one suit related to the deregulation of GE alfalfa. The USDA lost at trial in each case, with each judge ruling that the USDA was not sufficiently diligent in following the NEPA requirements.

In August 2006, Judge J. Michael Seabright of the Hawaii district ruled that APHIS failed to adequately consider the consequences of allowing field trials of GE corn and sugarcane on the state's many endangered species. On February 5, 2007, Judge Henry Kennedy of the Washington DC district court ruled that the USDA ignored evidence of potential environmental harm in allowing field trials of GE bentgrass. The following week, US District Judge Charles Breyer in California ruled that the USDA's FONSI decision on GE alfalfa was faulty, because he was not convinced that the data in the EA were adequate to reach a FONSI decision. Instead, he ruled that the USDA should have followed the more elaborate and extensive EIS route. To date, the USDA response to these rulings is only partially decided, but, if the court rulings are upheld, the agency will need to dramatically increase its regulatory scrutiny over GE plants.

Partly as a result of these lawsuits, and partly because of the ongoing review of regulatory procedures, USDA-APHIS has proposed a modification to the procedure leading to an EIS by moving to a multi-tiered system, in which GE plants are evaluated according to a progressively tiered presumption of risk. Thus, instead of having just two tiers (simple notifications and more substantial petitions), BRS will assign new GE plants into one of several tiers of increasing level of concern (and therefore increasing degree of regulatory scrutiny). The proposed changes also provide continuing regulatory oversight for those GE plants deemed to be unsuitable for non-regulated status. The proposed changes were open for public comment and subject to public discussion at open meetings in August 2007. More information on the proposed changes is available at http://www.aphis.usda.gov/publications/biotechnology/content/printable_version/fs_programmatic_eis.pdf.

Food and Drug Administration

The FDA has responsibility for ensuring the safety and security of human food and the supply of animal feed. The Center for Food Safety and Nutrition and the Center for

Veterinary Medicine evaluate new GE foods and feeds, focusing their attention on food and feed composition, looking for the presence of new or altered allergens and toxicants, and examining changes in levels of ordinarily present nutrients, fibre and other usual constituents.

The FDA probably has the greatest experience in dealing with GMOs, starting with the first commercialized GM product, human insulin (FDA approved Genentech's Humulin™ in 1982), and eventually the first food or feed product, Chymosin, for cheese making in 1990 (2 years after the same product was approved for commercial release in the UK). The FDA also handled the first approval for a whole food product, FlavrSavr™ tomato, in 1994.

In 1992, the FDA issued a policy statement establishing its authority under the Federal Food, Drug, and Cosmetic Act (FFDCA, 21 U.S.C. 301) to regulate new food and feeds, irrespective of the method of breeding (FDA, 1992). Under this policy, the FDA considers the food or feed composition relative to currently available counterparts, looking especially at the presence of allergens and toxins and any changes in the levels of nutritional and anti-nutritional substances. Foods containing unexpected or novel substances, or usual substances falling outside normal ranges for that kind of food, are considered as 'adulterated' and subject to FDA regulatory action. Foods and feeds identical or nearly identical in composition to regular versions are not considered as adulterated and do not trigger FDA review, even if they were produced using rDNA technology. The policy states that the FDA is concerned for feed and food safety, and that safety is a function of the substances present (or of the nutrients absent) from the food in question. If foods or feeds produced from or with GMOs are composed of the same substances and in the same amounts and relative proportions, there is no basis for a safety concern (above and beyond whatever safety concerns may ordinarily reside in that food or feed), and no need to invoke the 'adulteration' action trigger. This is why some individuals consider the FDA review to be 'voluntary'. Because most foods and feeds from GM plants are compositionally identical (or nearly so) to regular versions, the FDA does not require mandatory regulatory assessment. The FDA, in contrast with most other regulatory agencies worldwide, which trigger regulatory scrutiny based on the mere process of genetic engineering, regulates foods and feeds based on the objective changes in product composition. The FDA agrees with various scientific studies concluding that the *process* of genetic engineering is not inherently hazardous; therefore, the FDA does not compel new foods and feeds to undergo regulatory scrutiny merely as a result of the use of GE breeding methods. The FDA is almost unique in having

a scientifically sound basis for its regulatory trigger, recognizing that hazard is caused by the presence of tangible substances (or lack thereof), and not by the breeding method (McHughen, 2007).

However, *all* GM foods and feeds currently on the US market have undergone what is called an FDA 'consultation', in which the developer submits a dossier of compositional data relating to the putative 'identical' food or feed, and FDA scientists evaluate the composition in comparison with the composition of the regular foods and feeds. The data submitted include such information as the genetic stability of the plant, compositional analyses, nutritional assessment, and the allergenicity and toxicology of any substances ordinarily present in the food or feed, together with assessments of the introduced gene products. The FDA published guidelines to assist developers in compiling the dossier in 1997 (FDA, 1997). This procedure is beneficial to all parties, as it provides some assurance to consumers that a government agency is evaluating a new food or feed product prior to commercial release, it gives the developer an opportunity to have an independent third party (FDA) cast expert eyes over the data to ensure that no potential problems have been overlooked, and it keeps the FDA up to speed on new foods and feeds coming through the development pipeline. Even without compulsion, all developers of GM foods and feeds on the US market have completed the FDA consultation, largely because it is relatively simple, straightforward and prudent to do so. Nevertheless, some individuals have demanded that the FDA should adjust its policy to make the procedure mandatory. In practice, it already is.

Food and Drug Administration procedures

Because the FDA consultation is not legally codified, the process is informal relative to the procedures adopted by the other agencies, or by the FDA when regulating a new food or feed additive or a change in nutritional composition. The FDA is concerned with food and feed safety, and so the focus is on three starting questions: (i) does the new food or feed contain any new allergens?; (ii) does the new food or feed carry any new toxic substances?; and (iii) has the new food or feed an altered nutritional composition, such that the usual components are either increased or decreased? The proponent submits a dossier of data to the FDA consisting of a description of the modified food or feed, and the FDA assigns a caseworker familiar with that kind of food or feed to conduct the consultation. In addition to reviewing the compositional analysis, the caseworker might request information on expected dietary exposure, whether any risk groups (children, the elderly, pregnant women or immunosuppressed patients)

might experience increased or decreased dietary exposures, or, for a minor food, whether an increased dietary exposure may be experienced by any particular ethnic or religious groups. The FDA will consider both the expected changes in food and feed composition (e.g. the addition of a gene to enhance the levels of a particular nutrient) and the possibility that additional levels of this nutrient might result in a decline in the levels of other nutrients, especially precursors. Some critics of biotechnology argue that the unexpected changes in foods and feeds are the most worrisome, and such changes may be expected because rDNA is (to them) so 'unnatural' and destructive to the genome. Examples of such specious arguments are provided on the website of the Institute of Science in Society at <http://www.i-sis.org.uk/index.php>, or that of Jeffrey Smith at <http://www.seedsofdeception.com/Public/Home/index.cfm>. It should be noted that the 'unnaturalness' argument has no support from peer-reviewed scientific publications, and that these websites and their authors have little or no credibility in the scientific community.

So far, the FDA has not identified any examples of biotech foods with unexpected changes in nutrient composition, or in the levels of naturally occurring allergens, toxicants or other anti-nutritional substances ordinarily found in the same type of food (NAS, 2004a).

Indeed, recent studies on transgenic wheat have shown that rDNA transformation causes fewer changes to the plant than are seen in near genetically identical sister lines (i.e. progeny of cross-pollination with the same parents) that have not undergone rDNA transformation (Baudo *et al.*, 2006; Shewry *et al.*, 2007).

A more legitimate concern – technically – is that the inserted gene will produce an allergenic protein. No scientist would consider transferring a known allergenic gene into a food. Fortunately, the chance of unintentionally transferring an allergenic gene is small, as genetic engineers are aware of the issue and seek to avoid using allergenic sources for the genes. In any case, the FDA has allergens at the top of its checklist, so that a GE food carrying a new allergen is unlikely to ever get to market. Indeed, GE plant breeders have developed a soybean carrying an allergenic protein from Brazil nut. The intent was to enhance the nutritional profile of soy using the methionine- and cysteine-rich storage protein gene from Brazil nut, but it was not known at the time that the associated protein was also allergenic. The resulting GE soybean produced the relevant protein and showed an improved nutritional profile; however, early testing revealed the allergenic nature of the transferred protein and the project was terminated well before commercial release (Nordlee *et al.*, 1996).

If such an event were to occur, it would be discovered by the first consumers with the relevant allergy; the alarm would be sounded and the damage would be minimized. The company responsible would face sanction from the FDA for releasing an adulterated food (according to the definition), but this punishment would probably be insignificant compared with the wrath of litigation from the unsuspecting consumers suffering an allergic reaction from the ingestion of a previously safe food. With the pragmatic regulatory approach adopted by the FDA, and with the potentially disastrous consequences of bypassing the 'voluntary' FDA consultation, a GE food developer would be foolish not to seek the FDA's review.

It is worth noting that the FDA does not formally 'approve' an application, or even pass judgement on the safety or efficacy of the new product. Instead, the FDA issues a 'memo' summarizing the features and how they may affect safety concerns. The 'memo' indicates that the new food or feed is not materially different in composition or in respect of safety from the unmodified version of the same food or feed. That is, the FDA does not conclude that: 'This new food/feed is safe'. Instead, it concludes, based on the evidence reviewed, that: 'This new food/feed is as safe as its non-modified counterparts'. To date, the FDA has completed its consultation on almost 100 new GE foods and feeds.

Environmental Protection Agency

The EPA enjoys broad regulatory authority over substances with pesticidal characteristics, with particular concern for threats to human health and the environment. In addition to regulating the pesticides themselves, the EPA regulates according to changes in pesticidal properties or pesticide usage. Importantly, the EPA claims not to regulate GE plants *per se*, but rather it regulates the pesticidal *properties* associated with a GE plant. This trigger captures plants, such as GE virus-resistant plants, even though there is no pesticidal substance necessarily sprayed (or synthesized internally), as well as the more obvious herbicide-tolerant GE plants, where the crop is designed to be sprayed with a new pesticidal substance, such as the Roundup Ready™ group of crop cultivars. The EPA also captures GE plants which produce their own substances with pesticidal properties, the plant-incorporated protectant (PiP), which means GE plants expressing, for example, *Bt* or other insecticidal substances.

The EPA was given authority to regulate the pesticidal properties in GM plants under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) (7 U.S.C. s/s 135 et seq. 1972) and FFDCa. Under the co-ordinated framework, the EPA published its proposed regulations in 1994 and began acting

on them in 1995. The EPA's working definition of a PiP is 'a pesticidal substance produced in a living plant and the genetic material necessary for the production of that pesticidal substance, where the substance is intended for use in the living plant' (NRC, 2000).

In 1994, the EPA proposed the exemption of several low-risk categories (<http://www.epa.gov/pesticides/biopesticides/regtools/biotech-reg-prod.htm>). One category was plant pesticides in which the genetic material originated in a sexually compatible species. That is, if the pesticidal trait could be crossed through ordinary breeding, the resulting novel pest-protected plant would be exempt under FIFRA. A second exemption category included plants using physical barriers (and similar mechanisms such as inactivating toxic substances) to preclude the pest from attaching to or invading the plant. The third category included plants expressing viral coat proteins as a means to provide virus resistance. The proposals also included language to circumvent, as required under FFDCa, the establishment of a tolerance limit for such substances (NRC, 2000).

By 2001, the EPA had issued final rules exempting the previously captured sexually compatible PiPs, as well as exemptions for residues of the pesticidal substances and genetic material (DNA, RNA). The other proposals for exemption remained under review. Recently, the EPA has reiterated its desire to exempt virus resistance in plants produced by viral coat proteins because, with the gain of time and experience lending credibility to the scientific community's prediction that GM plants with these pesticidal properties are unlikely to cause problems, the EPA does not need to routinely capture for full regulatory assessment every similar such plant in future. That is, initially, the EPA invoked the novelty and lack of familiarity of virus-resistant viral coat protein GM plants to capture and assess all such plants prior to commercial release. With the intervening years of experience and familiarity with such products, the exemption proposed 13 years ago now has greater credibility. The exemption proposal is currently open for public comment.

Environmental Protection Agency procedures

In accordance with the co-ordinated framework, the EPA evaluates each submission on a case-by-case basis, so that the focus of concern with novel herbicide uses will differ from that with novel insect protection. To date, all GM PiP plants evaluated by the EPA produce proteins, mainly *Bt* and viral resistance proteins, such as coat proteins. In addition to data requirements related to product characterization, the EPA also demands data on mammalian toxicity, the effects on non-target organisms and environmental metabolism. For *Bt*

products, the EPA also demands an insect resistance management programme. For herbicide-resistant GM plants, the EPA co-ordinates with the USDA and FDA. The EPA emphasizes that it does not regulate the GM plant *per se*, but the herbicide used on or with the GM plant. For example, with a Roundup Ready™ soybean cultivar, the EPA does not evaluate the soybean plant alone; it evaluates the use of glyphosate (the active ingredient in Roundup™ herbicide) on the new soybean cultivar. Resistance management programmes are conducted under a 'Memorandum of Understanding' (MoU) with the other agencies.

The data requirements of the EPA are similar to those of other agencies, notably the USDA and the Canadian Food Inspection Agency, as they relate to the risks associated with particular substances. The dossier begins with a description of the plant and its modification. The EPA focuses on the pesticidal properties, so that EPA officials need to know the organic source of pesticidal gene construct, together with the promoter, enhancer, terminal region, etc. and a description of any marker genes or other segments on the inserted DNA. The biology and any relevant information on the recipient plant species is included, particularly information regarding the anti-nutritional substances produced by the plant or its associated pests, pathogens, weeds and relatives.

Genetic integrity and stability data on the inserted DNA are required, using molecular techniques, with emphasis on the number and location of insertion loci and stability over several seed or vegetative generations.

The pesticidal protein must be fully described (including the amino acid sequence) and characterized biochemically, including the expression pattern and intensity in various tissues or organs using standardized molecular/biochemical assays. Any modification to the protein, whether intentional (e.g. base changes for codon optimization or amino acid sequence alteration) or unintentional (e.g. glycosylation) also need to be reported. Mammalian allergenicity is an issue of concern because most PiPs are proteins and, as most allergens are proteins, give rise to concerns for allergenicity. Simple acute digestibility assays and amino acid sequence homology comparisons usually provide sufficient evidence to clear most such proteins from allergenicity concerns, but those failing these tests become subject to more elaborate, longer term immunological or feeding trials. The first step in assessing potential allergenicity is the species source of the transferred gene. That is, does the source organism produce allergens (e.g. soybean, peanut or fish) that will raise a red flag to justify further investigation? The amino acid sequence of the protein can be searched and compared against known allergens in a database and, again, depending on the degree

of homology (or sequence similarity), the suspect food can trigger greater scrutiny and, ultimately, human trials. Most GE foods do not reach this stage and are either deemed innocuous at an early stage or, if not, dropped from further progression towards commercial release.

Like APHIS at the USDA, the EPA is also concerned with gene flow issues. However, unlike the USDA, where gene flow interest is driven by concern for a potential increase in weediness or plant pest characteristics, the EPA's interest in gene flow is a result of the possibility of expanding exposure to novel pesticidal substances. The EPA is required by FIFRA to consider adverse environmental impacts attributable to possible gene flow, and by FFDCA to exempt or issue tolerances for the pesticidal substances that might enter the food and feed supply. So far, the EPA has analysed several plant species with *Bt* constructs and all have received exemptions. However, the EPA has prohibited the unregulated sale and cultivation of *Bt* cotton in some areas (Hawaii, Florida, Puerto Rico and the US Virgin Islands), because of the local presence of interfertile relatives or feral cotton populations, as they represent a recipient sink and opportunity for greater uncontrolled *Bt* exposure.

By the same reasoning, EPA seeks to preclude gene flow between GE plants and wild or feral relatives, as this is a primary means of gene escape, invasion and possible establishment of undesirable plants. This policy to date has not posed great hardship (except, possibly, to growers in Hawaii, Florida, Puerto Rico or the US Virgin Islands wishing to grow *Bt* cotton), but may take on greater significance with the increasing interest in biofuels made from GE versions of energy crops such as switchgrass. At present, in spite of considerable research and development of technologies to limit gene flow (via, for example, pollen disabling genes), no such gene flow mitigation technology is 100% effective (NAS, 2004b).

The EPA is also concerned with the effects of PiPs on non-target organisms in the environment. The requirements here involve an initial assessment of potential toxicity and exposure to non-target species, followed, where warranted, by up to four tiers of testing on the relevant species, according to EPA's Office of Prevention, Pesticides and Toxic Substances Harmonized Pesticide Test Guidelines.

Finally, the EPA considers the environmental fate of PiP substances, for example *Bt* in the soil, and how soil biota respond to *Bt* deposited by transgenic plant roots, decaying leaf matter, pollen settling, etc.

The EPA is sensitive to organisms – particularly insects – developing resistance to pesticides, and therefore considers management strategies to minimize and delay the onset of resistance in pest populations. Pests are known to develop

such resistance to pesticides, antibiotics and other such substances based on exposure and intensity. Because *Bt* is an important insect control chemical to many farmers – even organic farmers – the onset of resistant insect pest populations is a concern for all. The EPA takes the lead in requiring appropriate insect resistance management (IRM) strategies, and farmers are required to follow the IRM practice regulations. For *Bt*, these practices include areas of on-farm refugia to allow *Bt*-sensitive and *Bt*-resistant insects to mate in the absence of *Bt* selection pressure. The exact size and locations of the refugia will vary depending on the crop, the particular pest and the nature of the pesticide being used. Other factors, such as nearby alternative refugia or PiP crop species, may also influence the optimum presentation of the refugia.

Conclusions

The USA has an elaborate but co-ordinated regulatory system to evaluate new crops and foods. The scientific basis for assessing risks, combined with the co-ordinated framework assigning regulatory responsibility, gives the USA a functional, if imperfect, bureaucracy to allow environmental and market release of agricultural products of biotechnology.

This is not to suggest that the US system is efficient or fair. Indeed, there are substantial inefficiencies and at least one important flaw in the US regulatory system. Most notably, the scientific community, both in the USA and around the world, has concluded that the use of the process of biotechnology as the trigger for regulatory scrutiny is scientifically invalid (McHughen, 2007). Instead, regulation should be based on the risks posed by the features of the product, not the process of breeding. The USDA, in particular, ignores the findings of the scientific community and also its own OSTP by using the process-based regulatory trigger, thus unnecessarily imposing significant regulatory requirements on some non-risky GE plants, and failing to capture occasional risky plants merely because they are not products of biotechnology.

In addition, the current regulatory policies create, perhaps unwittingly, an almost insurmountable barrier to low-risk GE plants and foods derived from small market and speciality crops because of the high financial cost of regulatory compliance and the low overall value from the small acreage or small market potential of the special GMOs. That is, the additional market value attributable to the improvements to the GE plant or crop is insufficient to justify the expenditure to meet regulatory demands. This is especially galling for those improvements widely regarded, even in regulatory offices, as being very low risk. GE plants with considerable

health or environmental benefits are denied market access, not because they present undue risk, but because the developer cannot afford to jump through unnecessary regulatory hoops that provide little or no confidence in product safety.

Nevertheless, at least some products of biotechnology have passed through the US regulatory bureaucracy since 1994, have been cultivated widely and consumed intensively, and still there are no documented cases of adverse effects on health or the environment from any approved product of biotechnology. Although the rapid adoption of biotech crops by farmers worldwide (Brookes and Barfoot, 2006) seems to suggest a potential problem, especially with herbicide resistance and the concomitant inevitability of weeds evolving herbicide resistance, one must place this concern in the context that conventional breeding also generates crops with novel herbicide resistance and, indeed, weeds with resistance to those herbicides. To a large extent, the appearance of weeds acquiring herbicide resistance from GE crops supports and consolidates the early scientific predictions from the OECD (1982, 1986), NAS (1983, 1987, 1989) and others that the risks associated with GE plants are the same as those from conventional breeding.

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