



ISB NEWS REPORT

AGRICULTURAL AND ENVIRONMENTAL BIOTECHNOLOGY

NOVEMBER 2009

SPECIAL ISSUE:
SELECTED TOPICS ON US AND EU AGBIOTECH REGULATION

APHIS Restructures Regulation of GE Organisms

Phill Jones

APHIS Restructures Regulation of GE Organisms1

Herding Unconventional Animals Along the Regulatory Trail4

Introducing Genetically Engineered Corn into European Markets Is a Real Grind7

Should Novel Organisms Developed Using Oligonucleotide-mediated Mutagenesis Be Excluded from the EU Regulation?9

Regulatory Harmony in the GE World?13

Important Notice for ISB News Report Subscribers15

In October 2008, the Animal and Plant Health Inspection Service (APHIS) announced plans to revise its regulation of the importation, interstate movement, and environmental release of genetically engineered (GE) organisms. According to the agency, a desire to keep pace with the increasing complexity of biotechnology inspired the most comprehensive revision of its regulations since they were established in 1987. APHIS derives its regulatory authority from the Plant Protection Act of 2000, which combined authorities of the Noxious Weed Act, the Federal Plant Pest Act, the Plant Quarantine Act, and other statutes.

Proposal to Expand Regulatory Scope

APHIS regulates the environmental introduction of certain GE organisms that might be plant pests. A “plant pest” is any living stage of any of the following organisms that can damage or cause disease in a plant or plant product: protozoan, nonhuman animal, parasitic plant, bacterium, fungus, virus, viroid, or other type of infectious agent. Most plants are not plant pests. APHIS proposes to extend its regulations to include GE organisms that are noxious weeds. A “noxious weed” is a plant or plant product that can damage crops, livestock, poultry, or other interests of agriculture, irrigation, navigation, public health, the environment, and the natural resources of the United States. Unlike plant pests, noxious weeds are always plants or plant products. Under the planned rule, APHIS could regulate non-living material derived from a GE plant, if the agency concluded that the material is likely to pose a noxious weed risk.

The proposed regulations exclude GE microbes regulated as biological control organisms by the Environmental Protection Agency under provisions of the Federal Insecticide, Fungicide, and Rodenticide Act. APHIS plans to retain exclusions for GE microorganisms produced by inserting foreign genetic material that is well characterized and contains only noncoding regulatory regions into a recipient microorganism that is not a plant pest.

Proposal to Eliminate Notification Procedure

APHIS currently regulates GE organisms using a notification process and a permit procedure for the importation, interstate movement, and environmental release of certain GE organisms. In 1993, APHIS added the streamlined notification system for GE organisms considered to be lower risk, based on the agency’s experience. APHIS issues permits for regulated activities ineligible for notification; permits are generally more restrictive than notifications.

APHIS proposes to abolish the notification procedure and rely entirely on a permit practice. The agency considers the current notification procedure to be too inflexible.

PUBLISHED BY

**Information Systems
for Biotechnology**

Virginia Tech
1900 Kraft Drive, Suite 103
Blacksburg, VA 24061

Tel. 540-231-3747
Fax 540-231-4434

Subscribe to and access archived issues of the ISB News Report online:

www.isb.vt.edu

Editor: Ruth Irwin
rirwin@vt.edu

ISB welcomes your comments and encourages article submissions. If you have a suitable article relevant to our coverage of agricultural and environmental applications of genetic engineering, please email it to the Editor for consideration.

The material in this News Report is compiled by Information Systems for Biotechnology, Virginia Tech. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the US Department of Agriculture or of Virginia Tech. The News Report may be freely photocopied or otherwise distributed for non-commercial purposes only, with attribution.

To achieve a rapid administrative turnaround, notifications have generalized performance standards, which can be difficult to interpret and enforce. Permits, on the other hand, include requirements customized for each case. As an example, one of the current performance standards for notifications relevant to environmental releases states that: "The field trial must be conducted such that (1) the regulated article will not persist in the environment, and (2) no offspring can be produced that could persist in the environment." A comparable permit condition might read: "After final harvest of the GE corn plants covered under this environmental release permit, the site will be monitored every four weeks for the emergence of volunteer corn seedlings for one year, and any emerging volunteer plants will be devitalized before they produce pollen. Records of the monitoring and management of volunteers must be maintained by the permit holder and made available to APHIS upon request." Tailored permit conditions can provide clarity for the regulators and the regulated.

APHIS plans to establish an expanded, multiple category permitting system for environmental releases. The agency would first assign environmental release requests into categories based on whether the GE organism poses a plant pest risk or a noxious weed risk. Then, the agency would perform a complete risk assessment to fashion appropriate permit conditions. APHIS would require additional oversight measures for organisms that it has had less experience with or organisms with the potential to pose elevated risks. APHIS has stated that the proposed system would increase transparency about how the agency regulates various types of GE organisms, and would allow greater flexibility by allowing the agency to reclassify GE organisms in light of new information.

Exemptions from Permit Requirements and Nonregulated Status

The current regulations allow APHIS to confer conditional exemptions from the requirement for interstate movement permits. Exemptions offer regulatory relief while enabling APHIS to retain oversight over specific GE organisms. APHIS proposes to add a new, streamlined process for determining conditional exemptions, which would be broadened to allow petitioners to propose conditional exemptions from the requirement for a permit for importation, interstate movement, or release into the environment.

APHIS also wants to revise regulations for the granting of nonregulated status to GE organisms. The agency confers this status to GE organisms no longer subject to APHIS' biotechnology regulations. A GE organism that receives nonregulated status does not require a permit or any other APHIS oversight specifically related to genetic engineering. Among process changes in the petitioning for nonregulated status process, the agency wants to clarify the standard used by APHIS' Administrator to determine whether a GE organism is approved for nonregulated status. The new regulations also would include a procedure for the revocation of an approval of nonregulated status.

Low-Level Presence of Regulated GE Plants in Seed or Grain

Sometimes, small amounts of regulated GE material become accidentally mixed

with commercial seeds or grain. The press has referred to such inadvertent contamination as a disaster. APHIS calls it LLP, low-level presence. Today, APHIS' regulations lack provisions detailing responses in the event of a low-level presence of regulated materials mixed into commercial crops, food, feed, or seed. When contamination occurs, the agency has honed its reaction based on the level of risk determined by a scientific assessment of the facts in each case. In some situations, APHIS has required remediation, such as a recall, destruction of a crop, or restriction of movement. On the other hand, APHIS may decide to take no remedial action if the agency determines that the occurrence of GE plant material poses no risk to plant health and the environment. Even in these cases, APHIS can pursue enforcement action against a company or individual for violations of APHIS regulations that resulted in contamination.

APHIS proposes to codify its policies about low-level presence into regulations covering compliance, enforcement, and remedial action. Analysis about corrective action would be safety-based; APHIS would not allow contaminated commercial commodities or seeds to be distributed if they were likely to pose a plant pest or noxious weed risk. The proposed regulation lists criteria that the agency would use to determine whether to impose remedial action. For example, APHIS may decide that it will not order remedial action if the agency has approved nonregulated status for a GE plant of the same species expressing nearly identical proteins or substances. APHIS has also outlined possible enforcement actions the agency may take in response to an unauthorized low-level presence of GE plant material.

Regulation of GE Crops that Produce Pharmaceutical and Industrial Compounds

Here, APHIS aims to develop a permitting system to allow the agency to determine and enforce environmental release confinement measures sufficient

to ensure that cultivation of GE plants would be unlikely to result in the introduction or spread of plant pests or noxious weeds. APHIS plans to treat GE plants that produce pharmaceutical or industrial substances like any other GE plant it regulates, rather than treat the plants differently based on intended use. APHIS would determine confinement measures case-by-case, based on the risk posed by the particular environmental release. Like current regulations, the proposed regulations would not prohibit the environmental release of GE plants ordinarily used for food or feed production, even though they synthesize drugs or industrial chemicals.

“...APHIS may decide that it will not order remedial action if the agency has approved nonregulated status for a GE plant of the same species expressing nearly identical proteins or substances.”

Revisions Spark Comments

APHIS published its proposed revisions in the October 9, 2008, issue of the Federal Register. The agency received more than 15,000 comments by the time that the public comment period closed on November 24. In response to requests for additional time, APHIS extended the comment period to March and then to June 2009.

With regard to APHIS' proposal to extend its reach, some suggested

that the inclusion of the noxious weeds category would render the scope too broad and encompass too many harmless GE organisms. Others asserted that even the expanded scope would be too narrow, allowing an exemption of GE organisms that should be regulated.

Would elimination of the notification process impede APHIS' efficiency? Some argued that it would create a burden for APHIS that would significantly delay responses to permit requests. Increased regulatory burden, some argue, does not correspond to the low risk posed by GE plants.

Several agriculture trade groups stressed that the low-level presence of GE material can damage foreign markets for US products. The North American Export Grain Association advised APHIS to establish criteria for low-level detection of regulated material and to ensure that developers would be subject to enforcement actions for violations of regulations. The USA Rice Federation suggested the addition of a requirement

for the maintenance of representative samples of the regulated article, which would aid an investigation into the extent of an accidental contamination. Some urged that APHIS should have a zero tolerance for GE material contamination. Others criticized the LLP regulatory policy criteria for focusing on the safety of the foreign gene and foreign protein, while failing to take into account environmental effects or gene flow that may result when GE material mixes with a traditional commodity or seed.

APHIS' position on GE plants that produce drugs or industrial chemicals provoked strong reactions. Many stated that they wanted APHIS to concentrate on the intended use of such GE plants and ban all environmental releases of GE

plants designed to produce compounds for pharmaceutical or industrial uses, particularly if the plant species is also used for the production of food or feed.

On April 29-30, APHIS hosted a public meeting to discuss its proposed revisions of the regulations. In his closing statement, Mike Gregoire, Biotechnology Regulatory Services Deputy Administrator, said that APHIS will evaluate all comments and then decide how to proceed. The agency may re-propose some or all parts of the rule, or issue a supplemental Environmental Impact Statement on proposed revisions.

The old rules will be around for a while.

References

1. APHIS (2008) Importation, Interstate Movement, and Release into the Environment of Certain Genetically Engineered Organisms. Federal Register 73, 60008- 60048 (October 9, 2008).
2. APHIS (2009) Proposed Revisions to APHIS Regulation of Genetically Engineered Organisms. Available at: www.aphis.usda.gov.
3. Schuff, S (2009) Trade Groups Weigh in on Biotech Rule. Available at: www.feedstuffsfoodlink.com (January 5, 2009).

*Phill Jones
Biotech-Writer.com
PhillJones@nasw.org*

Herding Unconventional Animals Along the Regulatory Trail

Phill Jones

In January 2009, the US Food and Drug Administration issued its final industry guidance on the regulation of genetically engineered (GE) animals under the new animal drug provisions of the Federal Food, Drug and Cosmetic Act (FFDCA). The agency sees at least five reasons for producing a GE animal. Genetically modified animals can be designed to produce human antibodies and other substances useful for human therapy. Scientists have been engineering pigs to

reduce the risk of immune rejection after transplantation of their tissues into humans. Engineering of food animals can provide benefits to consumers, such as leaner meat from livestock and pork with increased levels of omega-3 fatty acids. Efforts are underway to produce GE dairy cows with resistance to mastitis and to protect cattle from mad cow disease. Scientists are also engineering environmentally-friendly food animals that require less feed and leave less environmentally harmful waste. The FDA

must approve GE animals before they, or their unique products, are allowed on the market.

How do these engineering efforts fall within the purview of the FFDCA? It's a matter of interpretation. The FFDCA defines drugs as "articles (other than food) intended to affect the structure or any function of the body of man or other animals." The FDA views a recombinant DNA molecule introduced into an animal as a substance intended to affect the animal's structure or function and therefore fulfills the definition of an animal drug. The oversight covers recombinant DNAs designed to produce a GE animal for food, or to create a GE animal bioreactor that synthesizes therapeutic agents. To comply with the FFDCA, a developer of a GE animal must show that the DNA construct and any substances expressed from the construct are safe for the health of the GE animal. If the GE animal is intended for food, then the developer must also show that the animals are safe for consumption. In addition to compliance with the FFDCA, the developer must meet requirements for environmental review under the National Environmental Policy Act.

The FDA's review process focuses on the effect of a recombinant DNA construct within the GE animal, not on the rDNA molecule itself. "In most cases, the methods used to introduce a new rDNA construct into the germline of an animal do not control the site in the genome where the construct will end up," the FDA explains. "Therefore, animals derived from different introductions of rDNA constructs (referred to as 'transformation events') will likely have their rDNA constructs at different sites in the genome." Since the insertion site can affect the animal's health and the expression of any genes encoded within the rDNA construct, the FDA considers each animal lineage derived from a separate transformation event to contain a separate new animal drug subject to its own new animal drug approval. Another way of looking at the process is that an rDNA construct at a specific site in the genome is the subject of the new animal drug approval. Safety and effectiveness evaluations will focus on animals that have been generated to be as closely related as possible to the animals that will be used commercially. Moreover, a sponsor will have to show that following approval and use in commerce,

the construct and/or phenotype are stably maintained in a representative sample of animals.

The agency released draft guidance in September 2008 with a 60-day public comment period. Although the FDA received about 29,000 comments, the agency classified about 28,000 as form letters or simple, general statements about GE animals or the draft guidance. The vast majority opposed the genetic engineering of animals. The remaining 797 comments offered specific suggestions or criticisms of the guidance, and of these, the agency considered about 60 to be substantive. Some of the key issues raised in the comments were the adequacy and appropriateness of using new animal drug application provisions to exert regulatory oversight of GE animals; the need for allowing public input into oversight of GE animals; the need for interagency collaboration at the federal level and between federal, state, and local governments; and the adequacy of FDA's approach to address animal health and safety.

A significant number of comments focused on the issue of labeling food from GE animals. Citing the idea of a consumer's "right to know," most urged the FDA to establish mandatory labeling of food products from GE animals. Using contrapositive logic, the FDA doesn't see such a requirement as fitting within current law. According to the law, a food is misbranded if its labeling is false or misleading in any particular way. A label is misleading if it fails to reveal facts that are material in view of representations made or suggested in the labeling. The FDA has traditionally interpreted the scope of "materiality" to mean information about the attributes of the food itself. The FDA does not consider the methods used to produce bioengineered foods, including the genetic engineering of animals, to be "material" information. Labeling may be required if food from a GE animal differs from its conventional counterpart, for example, in its nutritional content.

Concerns about food labeling also greeted the FDA's 2008 release of guidance for animal cloning. Following years of review, the agency concluded that the composition of food products derived from cattle, swine, and goat clones, or their progeny, does not differ from food products of conventionally-bred animals, and that food derived from cattle, swine, and goat clones, or

their offspring, does not pose unique risks to consumers. The FDA announced that it will not compel labels to alert consumers that a product contains ingredients from cloned livestock or progeny.

Send in the Clones – Part Deux

The news that the FDA had no further food safety concerns about products from cattle, swine, or goat clones, or their progeny, apparently stunned European Union officials. One official said that it was strange that a regulatory agency would make such a decision in the absence of Congressional debate and the enactment of laws. In the US, the idea that lawmakers would preempt a federal agency from performing its duties seems strange—almost as strange as the shifting debates and lack of decisions about clones within the EU.

In September 2008, the EU Parliament urged the Commission to ban the cloning of animals for the food trade, citing reduced genetic diversity and potential risks to animals and humans. Adopted by 622 Members of the European Parliament with just 32 opposing, the proposal called for a European Union-wide prohibition on the cloning of animals, the farming of cloned animals or their offspring, the placing on the market of meat or dairy products derived from cloned animals or their offspring, and the importing of cloned animals, their offspring, semen and embryos from cloned

animals or their offspring, and meat or dairy products derived from cloned animals or their offspring. The call for a ban followed an assessment of the European Food Safety Authority, a disclaimer-ridden, cautious approval of cloning.

In June 2009, EU agriculture ministers agreed upon a set of new rules for food products of the offspring of cloned animals, which would be included in the category of regulated “novel foods.” The regulation of cloned animal products would include risk assessment by the European Food Safety Authority and approval by the European Commission. Supporters of the plan said that the rules would close a loophole; current EU law does not explicitly cover commercialization of cloned animal products. Nevertheless, the council’s decision sparked fears of an imminent invasion of clones stampeding into the European market.

In September 2009, the Commission agreed to forward, within one year, a report to the Council and the European Parliament on all aspects of food production from cloned animals and their offspring, along with a legislative proposal if appropriate. The European Parliament will have to decide whether regulation that could pave the way to cloned animal products is better than promoting a ban that may never be realized and no regulation at all.

References

1. Beary, B. (2009) Future Potential Conflicts: Concerns over Legal Vacuum with Food from Clones. Available at: europolitics.abccom.cyberscope.fr (June 25, 2009).
2. Council of the European Union. (2009) Proposal for a Regulation of the European Parliament and of the Council on Novel Foods and Amending Regulation (EC) No XXX/XXXX. Available at: register.consilium.europa.eu (June 17, 2009).
3. EU ministers leave open possibility of cloned food. Available at: www.expatica.com (June 25, 2009).
4. FDA (2009) FDA Releases Final Guidance on Genetically Engineered Animals. Available at: www.fda.gov (January 15, 2009).
5. FDA (2009) Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs: Final Guidance. Available at: www.fda.gov (January 15, 2009).

*Phill Jones
Biotech-Writer.com
PhillJones@nasw.org*

Introducing Genetically Engineered Corn into European Markets Is a Real Grind

Phill Jones

In April 2009, Monsanto Company initiated legal action in a German court against the decision to ban cultivation and sale of the company's MON 810 genetically modified (GM) maize. The GM maize, which carries the Yieldgard® trait for resistance to the European corn borer, had undergone review and approval for animal feed cultivation in the European Union in 1998. Nevertheless, German Minister for Food, Agriculture and Consumer Protection Ilse Aigner directed the Federal Office for Consumer Protection and Food Safety to prohibit the marketing and cultivation of MON 810 corn varieties. Aigner asserted that certain information revealed a justifiable basis to believe that the GM maize presented a threat to the environment.

Where is the new scientific information? Monsanto asked. A company spokesman said that the explanation that Monsanto had received from the German federal food safety agency contained no new scientific findings. The study cited by the agency had been examined by the European Food Safety Authority, the European Union agency responsible for analyzing risks for food and animal feed safety. The company urged that Aigner's decision had damaged its legal rights, because the European Union had deemed MON 810 to be safe. Monsanto hoped for a quick decision in the company's favor so that farmers could sow the maize for the 2009 harvest.

On May 28, 2009, the Higher Administrative Court in Lüneburg, Germany, rejected Monsanto's appeal to lift the cultivation ban. The court noted that German law only requires a prognosis of an abstract danger for human health or the environment. Although the prognosis must be based on new information and scientific findings, the law does not require a final evaluation of the studies. Moreover, the court said that a thorough assessment of the studies is not required, because exemplary precedents of a MON 810 ban have been set by Austria, Greece, France, Hungary, and Luxembourg. The court seemed to say that other

countries have banned MON 810, so Germany can ban it as well.

The six EU member states may lift their temporary bans if the European Commission finally approves MON 810 cultivation within the EU. For a brief time, the approval appeared to be a step nearer when the European Food Safety Authority reconfirmed the safety of Monsanto's YieldGard® insect-protected corn trait in June 2009. "MON 810 is as safe as its conventional counterpart with respect to potential effects on human and animal health," the agency concluded. The agency's GMO Panel also decided that "MON 810 is unlikely to have any adverse effect on the environment in the context of its intended uses." The positive report should have placed the burden on the European Commission to propose a renewal of the existing MON 810 approval for cultivation and an expanded approval to all other uses. However, in July the European Food Safety Authority announced that it had decided to review a report issued by Greenpeace and Friends of the Earth on the MON 810 case and, possibly, reconsider its position.

European Rules and Attitudes

The European Union has established a comprehensive set of rules for the cultivation of GM crops and marketing of food and feed that contain ingredients from GM crops. Growing a GM crop requires authorization following a rigorous safety assessment for possible effects on the environment and human health. A farmer who grows a GM crop must follow technical and administrative measures to ensure that the GM crop can coexist with conventional or organic farming without cross-fertilization. Any food or feed derived from a GM crop must be labeled as such to inform consumers, while rules on traceability aim to track a GM crop or a product made from a GM crop at all stages in the marketplace.

The EU's evolving rules present challenges to anyone who wants to grow a GM crop. In March 2009,

the EU's Environment Council considered the European Commission's proposal to lift national safeguard clauses that ban the cultivation of GM corn in Austria and Hungary. The Council rejected the Commission's proposal. "Maize line MON 810 was approved according to Directive 90/220/EC, which has since been replaced by Directive 2001/18/EC, which contains harmonized environmental risk assessment criteria for GMOs," the Council explained. "Maize line MON 810 has not yet undergone a procedure of re-assessment in accordance with Directive 2001/18/EC."

Some Member States simply reject the idea of growing GM crops. To accommodate this choice, Austria recently proposed an opt-out clause. Considered by the Environment Council, the proposal would add a provision to EU legislation that would introduce the right of an individual Member State to restrict or prohibit indefinitely the cultivation of authorized GM organisms in its territory. A prohibition would be justified by socio-economic criteria, rather than by safety assessments alone. Although the opt-out proposal was tabled in June 2009, the idea may be revitalized in the future.

For now, only GM maize MON 810 has passed the hurdles for cultivation in the EU; at that, the use of the crop is restricted to animal feed and limited applications as food ingredients. The EU has not approved another GM crop for cultivation for over 11 years, while more than 140 GM crops have been approved outside of the European Union. In 2008, only seven of the 27 European countries cultivated GM maize on a commercial basis.

European resistance to GM crops began in the early 1990s with the introduction

of GM seeds designed to increase yields. When consumers could not see a direct benefit, they focused on potential risks. Public concern about GM food and GM crops significantly affected the marketing of GM products in Europe. Following the 1998 moratorium on further authorizations of GM crops and products, some Member States, such as Austria, invoked a safeguard clause to temporarily ban GM products.

Although the majority of European consumers continue to view the application of gene technology in agriculture with skepticism, recent polls suggest that acceptance is on the rise. The European Commission's Eurobarometer polls indicate that about half of consumers accept gene technology, particularly when the technology can be linked with benefits for consumers and for the environment, such as decreased applications of herbicides and pesticides. While shopping, most European consumers do not actively avoid products that contain GM ingredients.

A shift in attitude can be seen especially in the United Kingdom, previously a hotbed of GM crop vandalism. A 2008 British Institute of Grocery Distribution survey found that 58% of respondents declared themselves neutral about GM food. The British Food Standard Agency performed a poll in late 2008 that also revealed a decline in consumer concerns about GM food. The UK's Institute of Grocery Distribution poll uncovered an attitude that biotechnology may be important to mitigate global food shortages and to mount a response to challenges of food production in the wake of climate changes.

In June 2009, the EU's Health and Consumer Protection Directorate-General

"...The EU's evolving rules present challenges to anyone who wants to grow a GM crop."

launched an independent evaluation of the EU legislative framework on GM food and feed. The final analysis is due in one year and will consider the protection of consumers' interests. The Directorate-General for the Environment is planning a parallel review on

rules covering the cultivation of GM crops. Since the evaluations will consider consumers' interests, the growing acceptance of agricultural biotech may clear the way for biotech companies and farmers who want to plant GM crops.

References

1. Achilles, D (2009) Higher Administrative Court Supports German Cultivation Ban for MON 810 Corn. USDA Foreign Agricultural Service GAIN Report. Available at: gain.fas.usda.gov (June 2, 2009).
2. European Food Safety Authority (2009) Applications (EFSA-GMO-RX-MON810) for Renewal of Authorisation for the Continued Marketing . . . Available at: www.efsa.europa.eu (June, 15 2009).
3. Harrington, R (2009) EU proposal for national opt-outs on GM crops. Available at: www.foodnavigator.com (June 22, 2009).
4. Hogan, M (2009) Monsanto Seeks End to German GMO Maize Ban for '09 Crop. Reuters. Available at: uk.reuters.com (April 22, 2009).

Phill Jones
Biotech-Writer.com
PhillJones@nasw.org

Should Novel Organisms Developed Using Oligonucleotide-mediated Mutagenesis Be Excluded from the EU Regulation?

Didier Breyer, Philippe Herman, Annick Brandenburger, Godelieve Gheysen, Erik Remaut, Patrice Soumillon, Jan Van Doorselaere, René Custers, Katia Pauwels, Myriam Sneyers and Dirk Reheul

In the European Union, genetically modified organisms (GMO) and genetically modified microorganisms (GMM) are defined respectively according to Directives 2001/18/EC¹ on deliberate release of GMO and 2009/41/EC² on the contained use of GMM. The definition of a GMO is both technology- and process-oriented. A novel organism will fall under the scope of the GMO Regulation only if it has been developed with the use of certain techniques. The EU Directives therefore include annexes that give additional information regarding the techniques that result in genetic modification, that are not considered to result in genetic modification, or that result in genetic modification but yield organisms that are excluded from the scope of the Directives.

The underlying idea is that some processes of genetic modification are potentially associated with risks. This approach is now challenged with the emergence of new techniques for which it is not always clear whether the resulting organisms shall be subject to the prevailing European GMO legislation or not. In a recent paper published in *Environmental Biosafety Research*³, we discussed in detail regulatory and safety

issues associated with the use of oligonucleotide-mediated mutagenesis and provided scientific arguments for not having organisms developed through this technique fall within the scope of the EU regulation of GMOs.

Oligonucleotide-mediated Mutagenesis

Oligonucleotide-mediated mutagenesis (OMM) is a technique used to correct or to introduce specific mutations at defined sites of an episomal or chromosomal target gene. OMM is also referenced in the literature under other names, e.g., targeted nucleotide exchange, chimeraplasty, oligonucleotide-mediated gene repair, or targeted gene repair. OMM is mediated through the introduction of a chemically synthesized oligonucleotide (single-stranded DNA oligonucleotide, chimeric RNA/DNA or DNA/DNA, RNA oligonucleotide) with homology to the target gene, except for the nucleotide(s) to be changed. The mechanisms of action at the molecular level are poorly understood, but DNA repair enzymes are involved, and the process involves primarily the activation of the mismatch repair and/or nucleotide excision repair

pathway. The oligonucleotide hybridizes at the targeted location in the genome to create a mismatched base-pair(s), which acts as a triggering signal for the cell's repair enzymes. The gene modification is induced directly and exclusively via the effect of the oligonucleotide itself, indicating that the process is a type of gene repair and not homologous recombination.

Potential Applications of the Technique

OMM has potential applications in fundamental research, medicine, agro-food and pest control. Mutations are introduced *in situ* (i.e., site-specific mutations) and can target any nucleotide sequence (regulatory, coding, or non-coding), for instance to inactivate a deleterious gene, to induce local modification in expression (by controlling elements which may lead to changes in the level of gene expression), or to change an amino acid in the corresponding protein, resulting in a protein with possible new properties.

In bacteria and yeast, OMM has been used successfully mainly as a tool to perform fundamental research on gene expression and regulation, aiming at better understanding of the possible mechanisms underlying the genetic modification. In general, this technique is not expected to have major applications in microorganisms.

OMM has been successful in restoring or knocking out wild-type genes in animal cells, creating mouse mutants by modification of embryonic stem cells, and in directing genetic improvement of livestock animals. The technique seems to offer the potential to correct point mutations in human gene therapy, for instance in monogenic inherited diseases and cancer. In many cases, however, there has been a disparity in the frequency or reproducibility of gene correction. The efficacy of delivery of the oligonucleotides into the nucleus,

the long-term stability or purity of these molecules, the genetic background of the receiving organism, and the nature of target genes are potential factors that may contribute to this variability.

Oligonucleotide-mediated mutagenesis is also applicable to plants. Successful *in vivo* gene modification has been demonstrated, notably in maize, rice, tobacco, and wheat, e.g., to create plants insensitive to the action of a specific herbicide. Commercial applications of this technique in plants could even be expected in the short term. BASF and Cibus recently announced that they had reached a significant research milestone for developing CLEARFIELD Production System plants in *Brassica* winter oilseed rape and spring canola using Cibus' patented Rapid Trait Development System (RTDSTM) to enhance the tolerance levels of spring canola plants to CLEARFIELD herbicides⁴.

Regulatory Issues Whin EU Context

The EU definition of GMO implies a division of organisms between GMOs and non-GMOs, according to the techniques involved. When considering OMM in the context of the GMO definition and the+ techniques already listed in the Directives, the following conclusions can be drawn:

- OMM must be considered as 'leading to genetic modification' in the meaning of the EU Directives.
- All reviews clearly indicate that the process is a type of gene repair and not homologous recombination.
- The technique does not involve the introduction or integration of new genetic material in organisms, but alters chromosomal or episomal sequences *in situ* in their natural genetic background. OMM should not therefore be considered as a recombinant nucleic acid technique

in the meaning of the EU Directives. We are also of the opinion that the nucleic acid molecules used in the technique (oligonucleotides) should not be considered recombinant nucleic acid molecules.

- OMM does not make use of any vector system. Delivery of the oligonucleotide in the cell can involve micro-injection or micro-encapsulation (in liposomes), although other techniques such as electroporation or particle bombardment are more commonly used.
- OMM can be considered as a form of mutagenesis, a technique that is excluded from the scope of the EU regulation.

Another important point to consider is that organisms developed through OMM in many cases could not be distinguished at the molecular level from those developed through “traditional” mutation techniques (using chemicals or ionizing radiations) or from wild-type organisms (when the introduced change results in the restoration of the wild-type sequence). Detection and traceability are key aspects in the EU regulatory system on GMOs, in particular for GMOs used as Food or Feed. As a consequence, adequate molecular methods must be available that enable the detection and identification of each GMO individually (the so-called “transformation event”). It is important to realize that techniques such as OMM that do not involve the introduction into the genome of foreign DNA sequences from other species could pose challenges for unambiguous detection and testing, and ultimately enforcement of the EU regulatory system.

Safety Issues

The reliability, efficacy, and reproducibility of OMM show a great variability, and further studies are needed to improve the efficiency of mediating mutations, the effectiveness of their detection, and the knowledge on the mechanisms of action at the molecular level.

Nevertheless, the main advantage of OMM is that in many cases it should theoretically be more precise than other mutational techniques (such as irradiation or chemical treatment) and recombinant DNA technology. OMM acts on specific genes in a very targeted manner and does not use integrative vectors, thus eliminating

the risk of inadvertent insertional effects (such as mutagenesis or transactivation) associated with the introduction of foreign sequences in the host cell genome. In consequence, OMM should lead to fewer unintended effects. The high specificity of the technique has been demonstrated in several studies, and the risk of potential unwanted mutagenesis has been shown to be very unlikely when the oligonucleotide structure and chemistry were properly designed. Altered genes are also stably maintained during mitosis and transmitted in a Mendelian fashion to subsequent generations.

Moreover, unintentional changes are possible with all conventional (such as traditional breeding) and biotechnological methods for genetic modification. The development of novel organisms through OMM is not expected to generate more unintentional changes or effects than those faced by organisms generated by irradiation or chemical treatment. The extent to which these changes and potential effects should be assessed differently in GMOs from organisms developed with “traditional” methods underlies part of the controversy surrounding the use of GMOs⁵.

Conclusions

The term “oligonucleotide-mediated mutagenesis” covers various experimental approaches, but always has one objective: the site-specific correction or mutation of a target gene mediated by a chemically synthesized oligonucleotide. Broadly speaking, the technique does not pose biosafety questions other than those associated with similar techniques already listed in the GMO Directives, and could be considered similar to mutagenesis, a technique currently excluded from the scope of the EU GMO regulatory framework. This vision is shared by the COGEM (the Dutch GMO biosafety advisory committee)⁶.

OMM is just one amongst several techniques (including Zinc Finger Nuclease technology, cisgenesis, reverse breeding, agroinoculation, grafting on GM rootstock, RNAi, synthetic biology) that are currently challenging the process-based approach followed in the EU to define a GMO. There have been for example scientific papers arguing for the exemption of cisgenic plants from the scope of the EU Directives⁷.

In this context, a Working Group has been

established recently by the European Commission to evaluate these techniques and to develop further guidance on how they should be considered in the context of the existing legislative framework and to make its findings available to the relevant competent authorities for further follow-up. Indeed, the final decision as to whether or not organisms produced by a specific technique should fall under the scope of the EU regulation on GMOs is ultimately a matter of political and legal choices.

Moreover, we think that without similar discussions at the international level, it is likely that the same products of emerging new techniques might be considered GMOs or not depending on the regulatory jurisdiction. For instance, in the United

States, modified plants developed through oligonucleotide-mediated mutagenesis have been declared non-GM by USDA APHIS. Such discrepancies should be avoided, as they would pose challenges for the international regulation of transboundary movement of GMOs.

Last but not least, it is important to realize that the outcome of these discussions is of utmost importance for developers of novel organisms and in turn may have ramifications for plant breeders, agro-industry development, and biomedicine in the European Union. In the absence of legal clarity, the commercial applications of new techniques may be restrained, owing to the complexity and associated high costs of applying GMO legislation in the EU.

References

1. EC (2001) Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. *Off. J. Eur. Union L* 106: 1-38
2. EC (2009) Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms. *Off. J. Eur. Union L* 125, 75-97
3. Breyer D, Herman P, Brandenburger A, Gheysen G, Remaut E, Soumilion P, Van Doorselaere J, Custers R, Pauwels K, Sneyers M & Reheul D (2009) Genetic modification through oligonucleotide-mediated mutagenesis. A GMO regulatory challenge? *Environ. Biosafety Res.* DOI: 10.1051/ebr/2009007
4. BASF (2009) BASF and Cibus achieve development milestone in CLEARFIELD® Production System. <http://www.basf.com/group/pressrelease/P-09-119> (accessed August 25th 2009)
5. Nielsen KM (2003) Transgenic organisms – time for conceptual diversification? *Nature Biotechnology* 21, 227-228
6. COGEM (2006) New techniques in plant biotechnology (COGEM Report CGM/061024-02). Commissie Genetische Modificatie, The Netherlands. <http://www.cogem.net/> (accessed August 25th 2009)
7. Jacobsen E, Schouten HJ (2008) Cisgenesis, a new tool for traditional plant breeding, should be exempted from the regulation on genetically modified organisms in a step by step approach. *Potato Research* 51, 75-88

Didier Breyer
Scientific Institute of Public Health,
Division of Biosafety and Biotechnology
Rue J. Wytmanstraat 14, B-1050
Brussels, Belgium
didier.breyer@iph.fgov.be

Philippe Herman, Katia Pauwels and
Myriam Sneyers
Scientific Institute of Public Health,
Division of Biosafety and Biotechnology
Brussels, Belgium

Annick Brandenburger
Université Libre de Bruxelles, IBMM-
IRIBHM
Gosselies, Belgium

Godelieve Gheysen
Ghent University,
Department Molecular Biotechnology
Ghent, Belgium

Erik Remaut
VIB, Department for Molecular
Biomedical Research and Ghent
University, Department of Biomedical
Molecular Biology
Ghent, Belgium

Patrice Soumilion
Université Catholique de Louvain,
Laboratoire d'ingénierie des protéines et
des peptides, Institut des Sciences de la
Vie, Louvain-la-Neuve, Belgium

Jan Van Doorselaere
KATHO, Departement verpleegkunde
en biotechnologie, HIVB, Roeselare,
Belgium

René Custers
VIB, Zwijnaarde, Belgium

Dirk Reheul
Ghent University, Department of Plant
Production, Faculty of Bioscience
Engineering, Ghent, Belgium

Regulatory Harmony in the GE World?

Koreen Ramessar, Teresa Capell, Richard M Twyman, Hector Quemada, and Paul Christou

For the last 10 years, the economic value of transgenic crops has grown steadily. Every year, more land is used to grow commercial transgenic crops than the year before, and more countries take their first tentative steps into the genetically engineered (GE) world¹. After a decade of hostility, particularly within the European Union (EU), people are talking more about the socioeconomic and environmental benefits of transgenic plants². The boogeyman under the bed is losing the ear of the public.

Now that the public at large is more open to considering the benefits of transgenic technology, we can at last turn our attention to a problem that is stifling development and ensuring that the discoveries of today take a long, long time to reach the field. This problem is not technical, not logistical, not agricultural, but political—there is a distinct lack of harmony among international regulations that relate to research, biosafety, and to the trade and use of transgenic crops^{3,4}. The EU is particularly fussy, and its inflexible system amounts to a moratorium on applying transgenic technology within its own borders. Furthermore, the conflict between EU and US regulations means that the import and export of commodities derived from transgenic plants is fraught with difficulties⁵.

Nowhere is this more apparent than in the laws and regulations governing the tolerance levels for GE material in non-GE food and in the labeling and traceability of GE products^{3,4}. The definition of what is considered GE and non-GE food varies from country to country, with the EU in particular demanding precise tolerance targets while other countries have more relaxed rules or no rules at all. In the US, Canada, and Japan, food and feed can be classed as non-GE even if it contains up to 5% GE material. In contrast, Australia, New Zealand, South Africa, Brazil, and China set the limit much lower, at 1%. The EU is even stricter, with most non-GE food required to contain less than 0.9% GE to qualify, and an even stricter 0.5% limit applied to GE organisms that have yet to be approved, but which have received favorable risk assessments.

The disharmony with regard to tolerance limits

reflects two different mindsets⁶. The European mindset is based on the concepts of precaution and the consumer's right to know. Stringent approval, labeling, and traceability standards apply to any food produced from or derived from GE ingredients. In contrast, the North American mindset is based on differences in the end product, and includes a voluntary safety consultation and voluntary labeling guidelines for GE food. Most other developed countries have introduced regulations that share features of both the EU and North American systems. A recurring problem is that developing countries often base their regulatory frameworks on models promoted by developed nations. But they do this without considering the potential socioeconomic impact of their decisions, i.e., the decisions are political rather than scientific, and they do not consider the impact on the health and well-being of their own populations.

The consequences of global regulatory disharmony become acute when considering imports and exports, particularly when food is imported from a country with relaxed laws into a country that is very strict. Such conflicts have already occurred with US imports into the EU, resulting in food and feed being impounded⁵, and are bound to get worse as more countries start growing transgenic crops. The potential for conflict is compounded by disharmonious regulations concerning the labeling and traceability of GE food. The USA, Canada, Mexico, Argentina, The Philippines, and South Africa have voluntary labeling practices, whereas the EU, Australia, New Zealand, China, Chile, Brazil, and Taiwan require the mandatory labeling of GE produce⁴. Still other countries, including Bangladesh, Egypt, and Kenya, have no requirements for labeling.

As the prevalence of GE crops continues to grow, we foresee real problems with the trade and use of food and feed if the regulations are not harmonized on a global level. US food exporters and biotech companies have already complained about the EU's slow and obscure approval process, and unjustified and illegal bans by individual EU countries on GE products approved by the EU as a whole, often in response to unfounded

claims by ‘pressure groups’. This ongoing dispute has been intensified by the EU’s introduction of mandatory labeling. The role of the World Trade Organization’s legal framework regarding trade in GE products (the Sanitary and Phytosanitary Agreement, and the Agreement on Technical Barriers to Trade) has played a significant role in stifling the opportunities offered by GE products³. Strict labeling, identity preservation and import requirements impose additional costs and reduce public confidence, which in turn affects trade.

The decline in US corn exports to the EU has been blamed on the EU’s strict approval and labeling requirements, with some EU countries banning GE products all together, even after they have been approved by the European Food Safety Authority (EFSA), the EU’s own regulatory agency. Developing countries have also been dragged into this dispute as both sides try to win their support. Many developing countries have banned GE products due to consumer and environmental concerns, only to find themselves excluded from markets and refused financial support from industrialized nations to conduct research and build human capital for biotech activities⁷.

In the decade since GE crops were first adopted, it is estimated that farmers have earned \$27 billion from the technology, split almost equally between developed and developing countries¹. As well as direct economic benefits, GE crops reduce pesticide use, and reduce the use of fossil fuels in agriculture². These benefits could be lost, or curtailed, if the regulations in different parts of the world are not brought into line, or at least made mutually

compatible. It is also important to base the global regulations on scientific principles rather than unrealistic expectations of risk avoidance³. Currently, many countries have in place regulations that erect unnecessary hurdles to the further development of the technology, especially developing countries where the benefits are most needed. One approach to circumvent this problem is ‘mutual recognition’, where countries agree to recognize each other’s regulations⁵; for example, the US and EU could agree

to allow imports of each other’s products (GE and conventional) produced and marketed under home regulations, giving consumers on both sides of the Atlantic the choice.

Perhaps if Europe and the US were to show such leadership, this type of compromise could be

rolled out globally. Whatever the case, as more and more countries cultivate GE varieties, and national and international bodies continue to promulgate diverging regulatory approaches, there is little doubt that a more harmonious future for GE food and feed regulation would be in the interests of all.

“...many countries have in place regulations that erect unnecessary hurdles to the further development of the technology...”



Further reading

1. James C (2007) Global status of commercialized biotech/GM crops: 2007. ISAAA Brief No. 37. (ISAAA, Ithaca, NY, USA)
2. Brookes G, Barfoot P (2006) GM crops: the first ten years—global socio-economic and environmental impacts. *ISAAA Brief No. 36*. (ISAAA, Ithaca, NY, USA)
3. Ramessar K, Capell T, Twyman RM, Quemada H, Christou P (2008) Trace and traceability – a call for regulatory harmony. *Nature Biotechnol* 26, 975–978
4. Ramessar K, Capell T, Twyman RM, Quemada H, Christou P (2008) Calling the tunes on transgenic crops – the case for regulatory harmony. *Mol Breeding* 23, 99–112
5. Bernauer T (2005) Causes and consequences of international trade conflict over agricultural biotechnology. *151* 7, 7–28
6. Gruère GP (2006) A preliminary comparison of the retail level effects of labeling policies of genetically modified food in Canada and France. *Food Policy* 31, 148–161
7. Gruère G (2006) An analysis of trade related international regulations of genetically modified food and their effects on developing countries, EPTD discussion papers 147. International Food Policy Research Institute (IFPRI)

Koreen Ramessar¹, Teresa Capell¹, Richard M Twyman², Hector Quemada³ and Paul Christou^{1,4}

¹Departament de Produccio Vegetal i Ciencia Forestal, University of Lleida, Avenue Alcalde Rovira Roure 177, E-25198 Lleida, Spain

²Department of Biology, University of York, Heslington, York YO10 5DD, United Kingdom

³Department of Biology, Calvin College, 1726 Knollcrest Circle, S.E., Grand Rapids, MI 49546-4403

⁴Institutio Catalana de Recerca i Estudis Avancats

Important Notice for ISB News Report Subscribers



We are updating the distribution list for the ISB News Report. Please take a moment to indicate your subscription preference for the ISB News Report. Go to the ISB website at <http://www.isb.vt.edu>, and indicate your preference:

Email list

or

Print Copy

Email list subscribers will receive a monthly email notification when a new issue of the ISB News Report is published. The email will contain the table of contents with brief article summaries, and a URL link for accessing and printing the PDF.

Print copy subscribers **MUST** re-subscribe to continue to receive the ISB News Report by regular US mail. Those who have not re-subscribed to the ISB News Report Print copy will be purged from the mailing list in January 2010. Please note: We regret that the Print Copy option is available only to subscribers in the USA and Canada.

You may print current and archived issues of the ISB News Reports from our website. We maintain a searchable compendium of 1600+ News Report articles published since 1989.

Thank you for your continued interest in the Information Systems for Biotechnology News Report. Please let us know how we can improve our service to better serve your needs.

**ISB News Report
1900 Kraft Drive
Suite 103
Blacksburg, VA 24060**

**Non-Profit Org.
U.S. Postage
PAID
Blacksburg, VA
24060
Permit No. 28**