GM Crops & Food
Biotechnology in Agriculture and the Food Chain

ISSN: 2164-5698 (Print) 2164-5701 (Online) Journal homepage: http://www.tandfonline.com/loi/kgmc20

A new window of opportunity to reject process-based biotechnology regulation

Gary E Marchant & Yvonne A Stevens

To cite this article: Gary E Marchant & Yvonne A Stevens (2015) A new window of opportunity to reject process-based biotechnology regulation, GM Crops & Food, 6:4, 233-242, DOI: 10.1080/21645698.2015.1134406

To link to this article: http://dx.doi.org/10.1080/21645698.2015.1134406

GM Crops & Food, 6:233–242, 2015

ISSN: 2164-5698 print / 2164-5701 online
DOI: 10.1080/21645698.2015.1134406

A new window of opportunity to reject process-based biotechnology regulation

Gary E Marchant* and Yvonne A Stevens

Center for Law, Science & Innovation; Sandra Day O'Connor College of Law; Arizona State University; Tempe, AZ USA

ABSTRACT. The question of whether biotechnology regulation should be based on the process or the product has long been debated, with different jurisdictions adopting different approaches. The European Union has adopted a process-based approach, Canada has adopted a product-based approach, and the United States has implemented a hybrid system. With the recent proliferation of new methods of genetic modification, such as gene editing, process-based regulatory systems, which are premised on a binary system of transgenic and conventional approaches, will become increasingly obsolete and unsustainable. To avoid unreasonable, unfair and arbitrary results, nations that have adopted process-based approaches will need to migrate to a product-based approach that considers the novelty and risks of the individual trait, rather than the process by which that trait was produced. This commentary suggests some approaches for the design of such a product-based approach.

KEYWORDS. biotechnology, regulation, process-based, product-based, gene editing

From the beginning of the modern era of biotechnology, a central policy question has been whether regulation should be process-based or product-based. A process-based regulatory system differentiates regulatory requirements based on the process used to make the product. A product-based approach bases regulatory requirements on the characteristics of the final product, regardless of the process by which it was made. A key assumption of a process-based approach is that products made using the regulated process are fundamentally different or more risky than similar products made using other methods. In the case of genetically modified organisms (GMOs), a process-based approach thus assumes that products made using genetic engineering are more risky than comparable products made using other methods (Breyer et al., 2009). Such an assumption is contrary to the well-established scientific consensus that GMOs as a category are no more dangerous than conventional foods or foods produced by any other process (National Research Council 2004).

Different jurisdictions currently apply different approaches to this fundamental regulatory question. The European Union (EU) explicitly adopted a process-based regulatory regime, the United States endorses a product-based approach in principle but mostly applies a de facto process-based approach, and Canada has adopted an explicitly product-based strategy. Jurisdictions adopting a process-based approach typically apply a binary regulatory regime system that differentiates transgenic products

*Correspondence to: Gary E Marchant; Email: gary.marchant@asu.edu
Received September 1, 2015; Revised December 13, 2015; Accepted December 15, 2015.

from conventional products, generally leaving conventional products unregulated while imposing burdensome regulatory requirements on GMO products.

The regulation of GMOs is about to get much more complicated with the advent of various other techniques for modifying products, including genetic editing with engineered nucleases technologies such as CRISPR, but also other methods including cisgenesis, intragenesis, cell fusion, and RNA interference (RNAi). Nations that are currently applying a process-based regulatory approach are already facing scientific criticism for differentiating similar products made with different processes based on political and public perception rationales rather than scientific evidence (McHughen 2007). With the recent proliferation of new modification technologies, the credibility and feasibility of process-based approaches will be further challenged and may no longer be scientifically and politically sustainable.

In this article, we first trace the development of a partial or completely process-based regulatory approach in the EU and US based on a binary differentiation between transgenic and conventional products, and contrast these systems with a product-based system like Canada's. We then discuss how emerging new genetic modification techniques will undermine dualistic process-based regulatory frameworks. These existing regulatory regimes will need to change in response to these technological developments – we advocate transition to a purely product-based approach in the interests of sound science, administrative coherence, and fairness.

PROCESS-VERSUS PRODUCT-BASED REGULATION

Europe

Every jurisdiction that has considered the regulation of genetically modified products has had to confront the choice of adopting a product-based or process-based approach. The EU is a leading example of applying a process-based approach. While GMOs were initially categorized with foods made with other new technologies under the EU's novel foods regulatory category, in 2003 the EU adopted new Regulations that were specific to genetically modified (GM) foods, feeds and crops (EU Parliament and Council, 2003, n.d.). These Regulations, which took effect in 2004, applied different and much more rigorous requirements to any product produced using genetic engineering than other foods, feeds, and crops, even when expressing similar traits. The Regulations incorporate the definitions from EU Directive 2001/18/EC on the deliberate release of GM organisms and specifically apply to "recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation," and specifically exclude mutagenesis from the scope of the Regulations. Products that involve recombinant DNA are subject to burdensome pre-market risk assessment and approval, labeling and traceability requirements, which do not apply to other products such as those produced by mutagenesis.

United States

The US initially endorsed a product-based approach, concluding that products made with modern biotechnologies present no novel or increased risks as a category than equivalent products made with other techniques. The foundational document for the regulation of biotechnology in the US was the Coordinated Framework for Regulation of Biotechnology, adopted by the White House Office of Science and Technology Policy in 1986, which parceled regulatory authority for GMOs among the Food and Drug Administration (FDA), Environmental Protection Agency (EPA), and US Department of Agriculture (USDA) (U.S. Office of Science and Technology Policy 1986). This document instructed federal agencies to implement product-based regulation, stating that "[t]he manufacture by the newer technologies ... will be reviewed by FDA, USDA and EPA in essentially

the same manner for safety and efficacy as products obtained by other techniques" (U.S. Office of Science and Technology Policy 1986). The US National Academy of Sciences likewise advised in 2002 that "properties of a genetically modified organism should be the focus of risk assessments, not the process by which it was produced" (National Research Council 2002).

Yet, the US system diverged from a product-based approach in significant ways. The USDA initially classified all GMO crops as potential plant pests under the Plant Protection Act based on the presence, especially early on, of DNA sequences from potential pathogens, such as the cauliflower mosaic virus, and use of known pathogen vectors, such as agrobacterium tumifaciens (AT), in the genetic engineering process. AT causes crown gall disease in certain flowering plants. The USDA approach has resulted in significant costs and delays as developers of GMO crops have been required to go through a permit or notification process before field testing their products, and an even more expensive and time-consuming deregulation petition process before commercially introducing their GMO product. Crops with similar traits that were not made using transgenic methods were not subject to these requirements, providing a significant regulatory advantage to non-GMO products. Only in recent years have a handful of GMO products been able to avoid USDA regulation by using genetic constructs that did not use any DNA from any potential plant pest (McGinnis et al., 2012).

The EPA, through the Federal Insecticide, Fungicide, and Rodenticide Act regulates, among other things, plant-incorporated protectants (PIPs). These are pesticides produced by genetically engineered plants, genetically engineered to produce the active pesticidal substance. The EPA's regulatory authority extends only to the expressed substance and its genetic material, not the plant itself. EPA oversight is, therefore triggered by process: that of genetically engineering a plant to produce a pesticidal substance. A comparable plant engineered using non-recombinant DNA methods that has enhanced anti-pest traits would likely not be subject to EPA regulation. Moreover, EPA regulates inter-generic genetically engineered microbes under the Toxic Substances Control Act, imposing regulatory requirements that are triggered by the process of genetic engineering.

The FDA is the US agency that has most closely adhered to the product not process approach espoused by the US government. In adopting its policy toward GMOs, the agency stated:

> FDA's implementing regulations, and current practice, utiliz[e] an approach identical in principle to that applied to foods developed by traditional plant breeding. The regulatory status of a food, irrespective of the method by which it was developed, is dependent upon objective characteristics of the food ... [T]he key factors in reviewing safety concerns should be the characteristics of the food product, rather than the fact that the new methods are used. (Food and Drug Administration, 1992)

Yet, even the FDA has slid into a process based approach by suggesting that GMO producers "voluntarily" undertake an "informal consultation" with FDA prior to marketing new GM foods, which every GM food product to date has been subjected to. This results in significant extra costs and delays for GM products that do not apply to non-GMO products.

Canada

Unlike the EU and US, Canada has adopted a strictly product-based regulatory approach. GM crops and food in Canada are regulated by the Canadian Food Inspection Agency (CFIA) and Health Canada pursuant to the Seeds Act (Seeds Act, R.S.C 1985) and Regulations and the Food and Drugs Act and its Regulations (Food and Drugs Act, R.S.C 1985). To better align itself with the rapid progression of genetic engineering methods, the Canadian regulatory system identifies and distinguishes itself via 2 main concepts: 1) novelty; and 2) product, not process. This means that regardless of the modification method employed (i.e. mutagenesis, conventional cross-breeding, transgenesis, etc.), only plants with "Novel Traits" and foods

categorized as "Novel Foods" are subject to regulatory scrutiny (Smyth, McHughen 2008).

A plant with a novel trait (PNT) is one that has been subjected to the intentional introduction of one or more traits whereby the trait or traits is or are "new to cultivated populations of the species in Canada" and has or have "a potential to affect the specific use and safety of the plant with respect to the environment and human and animal health" (McAllister, 2013). A novel food is identified as a "substance, including a microorganism, that does not have a history of safe use as a food" or a "food that has been manufactured, prepared, preserved or packaged by a process that has not been previously applied to that food, and causes the food to undergo a major change." To enter the marketplace, PNTs must pass the stringent safety assessments imposed by the CFIA and Health Canada which ensure the PNTs are as safe for use as the conventional plant types already being cultivated. In terms of shared agency responsibility, the CFIA assesses PNTs used for livestock feed and their corresponding environmental impact, while Health Canada is charged with certifying that foods derived from PNTs are nutritious and safe for consumption (Canadian Food Inspection Agency).

The Canadian system promotes efficiency, coherence and uniform application of standards because no matter what technologies are used, regulatory intervention will apply only to novel plants and foods. This approach ensures that Canadian regulators do not selectively focus only on genetically engineered products even when similar traits are produced using other technologies, thereby avoiding the regulatory confusion and uncertainty currently being experienced by other process-focused nations.

It might be suggested that the Canadian approach is not strictly product based in that when it comes to food, regulatory assessment is required for food that has been, among other things, *manufactured by a process* not previously applied to that food, causing it to undergo a major change. Nonetheless, regulatory assessment is only triggered when the new process used causes the food to undergo a major change and exhibit a novel trait. Therefore, it is ultimately the characteristics of the product that are scrutinized and not the process.

THE DISRUPTIVE EFFECT OF NEW GENETIC MODIFICATION TECHNIQUES

One of the most important developments in the governance of genetic modification over the past few years has been the rapid proliferation of additional genetic modification techniques. This proliferation includes a variety of site-directed gene editing techniques using engineered nucleases, most notably clustered regularly interspersed short palindromic repeats with the associated Cas9 endonuclease (CRISPR/Cas9), but also including zinc finger nucleases and transcriptional activator-like effector nuclease (TALENs; Wolt et al., 2015). In addition to these gene editing approaches, other technologies that are now available for modifying microbes, plants and animals include cisgenesis (Telem et al., 2013), intragenesis (Lusser, Davies 2013), marker-assisted selection (Collard, Mackill 2008), grafting/ polyploidization (Fuentes et al., 2014), "molecular strengthening" (Hu, Lubberstedt 2015), RNAi (Kusaba 2004) and no doubt many others (now or in the near future). This array of new genetic modification technologies presents an existential challenge to process-based biotechnology regulation.

Governments, companies, scientists and nongovernmental organizations (NGOs) around the world are struggling to clarify how these new techniques "fit" into existing binary process-based regulatory frameworks that currently differentiate transgenic from "conventional" products (Wolt et al., 2015). Indeed, we are already seeing different process-based jurisdictions reaching inconsistent decisions on whether gene editing fits into the genetic engineering category, with Germany concluding it does and Sweden concluding it does not. This inconsistency, uncertainty and confusion overlays on and feeds into growing dissatisfaction with the current regulatory frameworks. Because site-specific gene editing techniques can make

genetic changes more precisely than traditional transgenic methods, they may justify less extensive regulatory oversight than transgenic products. Yet, the existing binary systems provide only 2 categories – transgenic and conventional products, leaving no room for some intermediate category. To complicate matters further, some "conventional" products created by mutagenesis may have similar traits as transgenic equivalents but involve even less precise and more promiscuous genetic changes, suggesting they should be regulated more stringently rather than less stringently than transgenic equivalents under a rational system that ties the level of scrutiny to the extent and imprecision of genetic changes (Schultz 2015).

To further complicate matters there is the growing list of genetic modification techniques described above in addition to transgenesis, gene editing, and mutagenesis. There is also variation within some techniques in potential risks based on factors such as the extent and type of genetic changes, the source of the genetic information, the specifics of the modification procedure, and characteristics of the host organism and its environment. For example, there are multiple gene editing techniques, which can each be used to make a variety of genetic changes ranging from deletions, to single base changes, to insertion of transgenic sequences (Wolt et al., 2015). Overlaying this technical complexity are social and political claims and controversies, including some NGOs contending that new genetic modification techniques are an industry strategy to avoid the regulations applicable to transgenic products (Pollack, 2015).

Regulatory agencies in the US and EU have struggled with trying to apply their existing binary transgenic/conventional regulatory framework to products modified using new techniques (Wolt et al., 2015). The USDA has responded on a case-by-case basis to a series of letters of inquiry from product developers, generally determining that the USDA regulatory requirements do not apply to products produced by gene editing and other non-transgenic methods (Camacho et al., 2014). While individual European countries have adopted inconsistent initial decisions on the regulatory categorization of gene editing techniques, the EU overall haso been indecisive to date about whether new techniques such as gene editing fall within the scope of its strict regulatory regime for GM products (Harvey 2014), with some scientists arguing that new techniques are more precise and should be exempted from the GM regulation (Breyer et al., 2009).

Some commentators and expert groups have tried to make sense of this chaos by proposing complex classification schemes that try to organize the various available processes into some sort of coherent hierarchy (Lusser, Davies, 2013). For example, Podevein et al. have proposed a 2-dimensional matrix that organizes products by the degree of gene editing change along one axis and the stability of the genetic modification along the other axis, creating 9 different potential categories (Podevin et al., 2012). This matrix only incorporates gene editing techniques, so an even more complex matrix would be needed to also incorporate other new genetic modification techniques.

These schemes are too complex and uncertain to provide the predictable and risk-based decision-making framework needed in this important and evolving field. Regulators, companies, scientists and NGOs all need a regulatory system that is consistent and predictable, and is robust in ensuring potentially risky products are given appropriate oversight while non-risky products are not unduly burdened with unnecessary regulatory hurdles. The continuum of available genetic modification processes resists any simple classification or categorization scheme. And the field is not static, there are likely to be new technologies or modifications and combinations of existing technologies that will require the constant reconsideration and updating of any process-based regulatory system. Moreover, as in other technology-rich fields, new evidence and learning will continuously arise, requiring a "learning" system that can adjust to the constant stream of new data (Institute of Medicine, 2012). It is critical to design regulatory frameworks that can keep pace with ever-changing technologies (Marchant et al., 2011). A static, fixed categorical system based on different processes is particularly unsuited to a dynamic, evolving field like biotechnology and crop modification.

A PATH FORWARD

As the previous section established, the proliferation of gene editing and other genetic modifications portends the end of any rational and credible process-based regulatory system, to the extent such a system was ever rational and credible. With the growing list of available genetic modification technologies, the existing binary transgenic-conventional process-based systems are obsolete, and any type of classification scheme that attempts to group and rank the continuum of different techniques will be unduly complex, unpredictable and inconsistent. Moreover, multiple modification technologies will increasingly be available to create products with the equivalent trait. This is already a problem in that crops with the same trait can be produced using different technologies, which undermines the scientific credibility of the regulatory system when these similar products are subject to vastly disparate regulatory requirements under the existing binary process-based system. As this overlap in end-products from different processes becomes more common, process-based regulation will become increasingly discredited (Morris, Spoillane 2008).

Regulatory systems will therefore have no choice but to ultimately migrate to a product-based rather than process-based approach (Wolt et al., 2015). By doing so sooner rather than later, governments can minimize the disruption, inefficiency and confusion undermining their process-based systems. This provides an important window of opportunity to consider a more scientifically-based and effective regulatory approach. The US government's recent call to reconsider the existing Coordinated Framework for Regulation of Biotechnology is an opportune window of opportunity to undertake the inevitable shift to a product-based system (Holdren et al., 2015). How should this product-based system be constructed in the US?

One approach would be to subject all modified products, regardless of what process was used to make them, to the existing regulatory requirements for transgenic products. This would ensure a rigorous regulatory review for all modified products, whether they were produced by mutagenesis, transgenesis, or new techniques such as gene editing technologies. Such an approach would also end the irrational result of similar products exhibiting the same trait but made by different technologies from being subjected to dramatically different regulatory requirements. It would also address concerns of some NGOs that companies would strategically utilize new modification technologies to evade regulatory requirements for transgenic products.

Applying the current transgenic system to all modified products would be enormously wasteful and counter-productive however. For transgenics themselves, it is increasingly apparent the current system is unduly burdensome, duplicative and wasteful, as almost 20 y of regulatory experience with rigorous scientific oversight has demonstrated few environmental or health problems from growing or eating transgenic products (Camacho et al., 2014). Regulators have now accumulated sufficient evidence and experience to predict with confidence that many transgenic crops and foods are safe, especially those with similar traits to products that have gone through extensive regulatory review. The extensive regulatory burdens for transgenic products have increased costs and delays for products that ultimately obtain regulatory approval, and have deterred many university, small business and public sector labs from pursuing transgenic products for humanitarian, non-profit or specialized market applications (Holdren et al., 2015). Expanding this existing overly-stringent regulatory system to other processes such as mutagenesis which has been exempt from regulation until now, and more precise techniques such as gene editing which can add foreign DNA more precisely than traditional transgenic methods, would only increase the inefficiency and lack of scientific rigor of the current system.

There are a couple additional reasons for moving toward less rather than more oversight of genetically modified products. First, one of the secondary objectives of extensive regulatory oversight of transgenic products was to increase public confidence in the technology. The current regulatory system is not achieving this goal, as public opinion seems to be growing increasingly anti-GMO rather than pro-GMO. For example, a

recent Pew study found that only 37 percent of the public believed that GMOs were safe to eat, compared to 88 percent of scientists, creating the biggest gap between scientists and the public on any of the science-policy issues considered (Pew Research Center, 2015). Studies with other technologies that have been subject to precautionary regulation find that such regulation stigmatizes the technology and increases rather than reduces public fears and anxiety (Wiedemann, Schütz, 2005).

Second, unnecessarily broad regulation triggers secondary regulatory requirements that can further increase regulatory costs and delays. Specifically, the requirement of regulatory approval is usually a "federal action" that triggers the National Environmental Policy Act (NEPA), which requires the regulatory agency to conduct an assessment of the environmental impacts of its proposed decision. This can trigger years of delays and millions of dollars of extra costs for the agency and affected company, as well as providing an opportunity for opponents to file a citizen suit to further delay the regulatory approval. GMO crops have been subject to repeated delays and nuisance lawsuits for procedural claims under NEPA (McGinnis et al., 2012). Therefore, the scope of regulation should be carefully limited to avoid snaring products in the NEPA web if there is no real need for regulatory oversight.

For these reasons, and given the long record of safety with GMO regulation, the new product-based regulatory system should start with a presumption of no pre-market regulatory approval for crops and food with existing traits, recognized as safe (Bradford et al., 2005). Specific types of products should be required to obtain a one-time pre-market approval for potential environmental or health risks (separate decisions by USDA and FDA respectively) based on red flags associated with the trait, *novel or otherwise*, rather than the process by which it was created. For example, a plant product engineered by any method to produce an active pharmaceutical should be subject to pre-market environmental review by USDA, because of the potential dangers if the active product were to get into the environment. Alternatively, an engineered plant-based food product from a crop modified with a gene from a known or potentially allergenic species should be subject to pre-market FDA review for food safety. An initial list of trait-based "red flags" that automatically trigger pre-market review by USDA for environmental impacts or FDA for human health (from food) impacts could be created, to be modified based on experience going forward. New PIPs not subject to previous regulatory scrutiny or which otherwise raise specific "red flag" concerns would continue to be evaluated and regulated by EPA, although its regulations would have to be reevaluated accordingly under the proposed red flag system.

If other unanticipated problems should be observed, USDA, FDA, and EPA could use post-market authority to take regulatory action (and perhaps revise the list of red flag categories to prevent future re-occurrences). Regulatory resources would be better spent on post-market surveillance, which can then focus on those rare products that do present health or environmental risks, rather than burdening all modified products, most of which likely present no significant risks.

If the proposed system of a presumption of no pre-market review is not politically feasible, a less radical proposal would be to adopt a novel trait based regulatory system. Very similar to the Canadian system, only crops and foods incorporating a *new* trait, differentiating it from our first proposal, would be subject to pre-market review and approval. Subsequent products expressing a previously approved trait would be fully or partially exempted from duplicative pre-market reviews, regardless of the technique by which they were produced (Smyth, McHughen, 2008).

The relaxation of pre-market review requirements for GM products should not affect a responsible company's ethical responsibility to appropriately test their products before commercialization. This does not mean conducting the full slate of tests currently required for regulatory approval of transgenic products, as many of these tests may be redundant or not indicated for a specific product or application. But a company should make a case-by-case determination of whether and what health or environmental safety tests are warranted,

regardless of whether the product is transgenic, genome edited, conventional, or organic.

Adoption of the more relaxed but scientifically sound regulatory approval system described here would likely raise 2 types of objections. First, anti-GMO activists would try to further undermine public confidence in GM foods by criticizing the lack of pre-market regulatory approval for many GM products. While such arguments may achieve some short-term traction, the effect in the long-run will be beneficial by reinforcing the well-established scientific consensus that GM crops and foods as a category are not more risky than comparable products made using other processes. The current regulatory system that selectively targets only GM products stigmatizes transgenic technology and has a long term corrosive effect on realistic public understanding of food safety.

The second concern is the effect of a new regulatory system on international trade. Foods and feeds are heavily traded in international commerce, and disparate regulatory approval criteria and status has already disrupted trade in GMO-containing commodities. If the new US product-based regulatory system becomes even more inconsistent with the process-based systems of many European and Asian nations, more trade disruptions are possible. But such concerns should not deter making the US system more science-based. First, the process-based systems in the EU, Asia and elsewhere already are causing major trade issues for the US, as those other jurisdictions delay or fail to approve new GMO products approved in the US. These trade disputes will only get worse with the proliferation of gene editing and other new genetic modification technologies, as nations adopt inconsistent process-based regulations. It is therefore not clear that the US adoption of a more rational product-based system would make trade problems any worse than they would be without such revisions.

Second, and most importantly, the only pathway to harmonious trade in new crop, food and feed products is to create a level regulatory field based on applying the best available science that focuses on real risks. The US can best advance such an approach at the international level by adopting such a system into its own domestic laws, and then encouraging other nations to follow suit. There have been increasing indications that governments and scientific organizations in other jurisdictions are recognizing the need to move away from discriminatory and unscientific process- based regulation. The proliferation of new genetic modification technologies such as gene editing is creating a promising window of opportunity to reconfigure biotechnology regulation at both the national and international levels.

CONCLUSION

The proliferation of new techniques for genetically modifying plants, animals and foods presents both a regulatory challenge and opportunity. Existing binary transgenic/conventional process-based regulatory systems in the US and EU will become increasingly stretched and scientifically undermined by trying to force the new technologies into their already outdated binary process-based regulatory frameworks. The new technologies will create a continuum of products that differ in potential risks by a variety of factors, of which process of production will increasingly become insignificant. This continuum of products will inevitably and eventually force governments to switch to a more scientific product-based system. Given the extensive historical record of safety and the growing knowledge about the safety of genetic modification techniques, this article proposes a new approach that includes a presumption of no pre-market regulatory review for existing, accepted traits, with certain categories of products being subject to health or environmental pre-market requirements based on non-static, evolving trait-based "red flags" of established or potential concern, that are independent of process used for production.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

REFERENCES

Bradford KJ, Van Deynz A, Gutterson N, Parrott W, Strauss SH. Regulating transgenic crops sensibly: lessons from plant breeding, Biotechnol Genomics 2005; 23:439-44

Breyer D, Herman P, Brandenburger A, Gheysen G., Remaut E, Soulmillion P, Van Doorsselaere J, Custers R, Pauwels K, Sneyers M, et al. Genetic moidification through oligonucleotide-mediated mutagenesis. A GMO regulatory challenge? Environ Biosafety Res 2009; 8:57-64; PMID:19833073; http://dx.doi.org/10.1051/ebr/2009007

Camacho A, Deynze Av, ChiHam C, Bannett AB. Genetically engineered crops that fly under the US regulatory radar. Nat Biotechnol 2014; 32:1087-91; PMID:25380439; http://dx.doi.org/10.1038/nbt.3057

Canadian Food Inspection Agency. The Safety Assessment Process for Plants with Novel Traits (PNTs). 2012. Available from http://www.inspection.gc.ca/plants/plants-with-novel-traits/general-public/assessment-process/eng/1338189630096/1338189929476

Collard BCY, Mackill DJ. Marker-assisted selection: an approach for precision plant breeding in the twenty-first century 2008; 363:557-72; PMID: 17715053

EU Parliament and Council, Regulation (EC) 1829/2003 on genetically modified food and feed. 2003. Available from http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32003R1829

EU Parliament and Council, Regulation (EC) 1830/2003 traceability and labelling of GMOs. n.d. Available from http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=URISERV:l21170

Federal Insecticide, Fungicide, and Rodenticide Act. 7 U.S.C. § 136.

Food and Drug Administration. Statement of policy: foods derived from new plant varieties. Fed Regist 1992; 57:22,983-23,001

Food and Drugs Act, R.S.C. 1985; c. F-27 (Can.)and Regulations. Available from http://laws-lois.justice.gc.ca/eng/acts/F-27/

Fuentes I, Stegemann S, Golczyk H, Karcher D, Bock, R Horizontal genome transfer as ab asexual path to the formation of new species. Nature 2014; 511:232-5; PMID:24909992; http://dx.doi.org/10.1038/nature13291

Harvey F. Genome editing of crops may be restricted by EU rules, warn scientists. Guardian 2014; July 21; Available from http://www.theguardian.com/environment/2014/jul/21/genome-editing-crops-restricted-eu-rules-scientists-warn

Holdren JP, Shelanski H, Vetter D, Goldfuss C. Memorandum for Heads of Food and Drug Administration, Environmental Protection Agency, and Department of Agriculture: Modernizing the regulatory system for biotechnology products. July 2, 2015. Available from https://www.whitehouse.gov/sites/default/files/microsites/ostp/modernizing_the_reg_system_for_biotech_-products_memo_final.pdf

Hu S, Lubberstedt T. Getting the 'MOST' out of crop improvement. Trends Plant Sci 2015; 20:372-9; PMID:25899781; http://dx.doi.org/10.1016/j.tplants.2015.03.002

Institute of Medicine. Best care at lower cost: the path to continuously learning health care in America. Washington, DC: National Academy Press, 2012.

Kusaba M. RNA interference in crop plants. 2004; 15:139-43; PMID:15081052

Lusser M, Davies HV. Comparative regulatory approaches for groups of new plant breeding techniques. New Biotechnol 2013; 30:437-46; PMID: 23474021; http://dx.doi.org/10.1016/j.nbt.2013.02.004

Marchant GE, Allenby A, Herkert J. (Eds.), The growing gap between emerging technologies and legal-ethical oversight: the pacing problem. Dordrecht, Germany: Springer, 2011.

McAllister P. *The Canadian regulatory process for plants with novel traits*, North American biotechnology council, NABC report 25: biotechnology and North American specialty crops: linking research, regulation, and stakeholders. Proc Twenty-Fifth Annu Conf N Am Agr Biotechnol June 2013 at 161. Available from http://nabc.cals.cornell.edu/Publications/Reports/nabc_25/25_4_4_McAllister.pdf

McGinnis EE, Meyer MH, Smith Ag. Analysis of U.S. genetically engineered crop regulation and litigation. Crop Sci 2012; 52:991-1002

McHughen A. Fatal flaws in agbiotech regulatory policies. Nat Biotechnol 2007; 25:725-7; PMID:17621292; http://dx.doi.org/10.1038/nbt0707-725

Morris Sh, Spoillane C. GM directive deficiencies in the European Union. EmBO Rep 2008; 9:500-4; PMID: 18516083; http://dx.doi.org/10.1038/embor.2008.94

National Research Council. Genetically modified pest-protected plants: science and regulation. Washington, DC: National Academy Press, 2002.

National Research Council. Safety of genetically engineered foods: approaches to assessing unintended health effects. Washington, DC: National Academy Press, 2004.

Pew Research Center. Public and scientists' views on science and society; 2015; Available from http://www.pewinternet.org/files/2015/01/PI_ScienceandSociety_Report_012915.pdf

Podevin N, Devos , Davies HW, Nielsen KM. Tramsgenic or not? No simple answer! EMBO Rep 2012; 13:1057-61; PMID:23154464; http://dx.doi.org/10.1038/embor.2012.168

Pollack A. By 'editing' plant genes, companies avoid regulation. NY Times 2015; Jan. 1.

Schultz D. GMO or no? New tech raises new regulatory dilemmas. Chem Reg 2015; Reporter (Bloomberg BNA), 39:1046, Aug. 31

Seeds Act, R.S.C. 1985, c. S-8 (Can.) and Regulations. Available from http://laws-lois.justice.gc.ca/eng/acts/S-8/

Smyth S, McHughen A, Regulating innovative crop technologies in Canada: the case or regulating genetically modified crops. Plant Biotech J 2008; 6:213-25; PMID:18028290; http://dx.doi.org/10.1111/j.1467-7652.2007.00309.x

Telem RS. Wani SH, Singh NB, Nandini R, Sadhukhan R, Bhattach RYS, Mandal N, Cisgenics – A sustainable approach for crop improvement. Curr Genomics 2013; 14:468-76; PMID:24396278; http://dx.doi.org/10.2174/13892029113146660013

U.S. Office of Science and Technology Policy. Coordinated framework for regulation of biotechnology; announcement of policy; notice for public comment. Fed Regist 1986; 51:23302-50; PMID:11655807

U.S. Office of Science and Technology Policy. Coordinated framework for regulation of biotechnology; announcement of policy; notice for public comment. Fed Regist 1986; 51:23304; PMID:11655807

Wiedemann PM, Schütz H. The precautionary principle and risk perception: experimental studies in the EMF area. Environ Health Perspect 2005; 113:402-5; PMID:15811829; http://dx.doi.org/10.1289/ehp.7538

Wolt JD, Wang K, Yang B. The regulatory status of genome-edited crops. Plant Biotechnol J 2016; 14(2): 510–518; PMID:26251102; http://dx.doi.org/10.1111/pbi.12444