Regulation of Plants with Novel Traits: Canadian Perspectives on the "Novelty" Trigger

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In determining whether a plant that is the product of gene editing would be regulated in Canada, it is important to consider whether the product would be considered to be novel. The following discussion will focus on Canada's product-based approach to assessing plants with novel traits (PNTs) for use as food, as feed, and for release into the Canadian environment. As the author works in the area of environmental release of PNTs, this will be the main emphasis.

Background Information on the Canadian Regulatory Authorities with Regard to Plants with Novel Traits and Products Derived from Them

Canada's product-focused system for regulating agricultural products of biotechnology relies on science-based safety assessments and risk management, with the overall goal of protecting human and animal health as well as the environment. This product-focused framework employs regulatory triggers to distinguish PNTs and novel plant products from their conventional counterparts.

The *Canadian Environmental Protection Act* (CEPA) requires that a person who wishes to import, manufacture, or sell any new substance must notify the appropriate Canadian regulatory authority, so that the new substance can be evaluated for potential effects on the environment and human health. To avoid duplication of regulatory oversight, CEPA exempts those products of biotechnology regulated under certain other acts and regulations

(*e.g.* the *Seeds Act, Feeds Act, Fertilizers Act*) from the requirement to notify Environment Canada. However, Environment Canada retains residual powers under CEPA to regulate any products or end-uses that other acts do not regulate.

Each act describes the powers held by the minister responsible for that act. Regulations are made under the authority of the enabling act, and define the application and enforcement of that act. For example, in the case of the *Seeds Act*, the responsible minister is the minister of Agriculture and Agri-Food. The minister's authority to authorize the environmental release of seed is defined in the *Seeds Regulations*, Part V, paragraph 111. To paraphrase the authority in that paragraph: after receiving and assessing all requisite information, and with consideration of risk to the environment, the minister will authorize release, imposing any conditions necessary to manage environmental risk. Refusing to authorize a release is within the minister's power only when the proposed release poses an unacceptable risk to the environment, or when the minister has reasonable grounds to believe the proponent will not respect the conditions imposed upon the release.

To provide guidance in the interpretation of the relevant acts and regulations, departmental documents, such as directives and guidelines, are often available. These documents are based on the legislation, but do not have the force of law.

Steps in the Regulatory Process in Canada

Regulatory Trigger

Canada takes a product-based rather than a process-based approach to regulation of products of biotechnology. The trigger for regulation in all cases is based on novelty. The responsibility to determine that a product may be novel rests with the proponent, while the final decision on novelty rests with the appropriate regulatory authority. A proponent may be unsure whether a product would be considered "novel." In these cases, a consultation with regulators to determine novelty is often a useful step. A full description of this process can be found here:
http://www.inspection.gc.ca/plants/plants-with-novel-traits/applicants/pre-submission-consultation/eng/1368394145255/1368394206548.

In brief, a novelty determination can involve a meeting between the proponent and regulators from Health Canada and the Canadian Food Inspection Agency (CFIA). The proponent will provide a description of the product. After evaluating the information provided, each regulatory authority will provide the proponent with their novelty determination.

The regulatory trigger is not identical for novel foods, novel feeds, and PNTs. It is, therefore, necessary to consider whether a product may be novel under each relevant set of regulations:

- *Food and Drugs Act and Regulations:* Health Canada
  More information on the assessment and regulation of novel foods can be found at: http://www.hc-sc.gc.ca/fn-an/legislation/guide-ld/nf-an/guidelines-lignesdirectrices-eng.php.

Definition of Novel Food from the Food and Drugs Regulations:

- *"Novel food" means*

  (a) a substance, including a microorganism, that does not have a history of safe use as a food;

  (b) a food that has been manufactured, prepared, preserved or packaged by a process that

  (i) has not been previously applied to that food, and

  (ii) causes the food to undergo a major change; and

  (c) a food that is derived from a plant, animal or micro-organism that has been genetically modified such that

  (i) the plant, animal or microorganism exhibits characteristics that were not previously observed in that plant, animal or microorganism,

  (ii) the plant, animal or microorganism no longer exhibits characteristics that were previously observed in that plant, animal or microorganism, or

  (iii) one or more characteristics of the plant, animal or microorganism no longer fall within the anticipated range for that plant, animal or microorganism.

- *"Genetically modify" means*

  to change the heritable traits of a plant, animal or microorganism by means of intentional manipulation.

- *"Major change" means*

  in respect of a food, a change in the food that, based on the manufacturer's experience or generally accepted nutritional or food-science theory, places the modified food outside the accepted limits of natural variations for that food with regard to

  (a) the composition, structure or nutritional quality of the food or its generally recognized physiological effects;

  (b) the manner in which the food is metabolized in the body; or

  (c) the microbiological safety, the chemical safety or the safe use of the food.

o *Feeds Act and Regulations: CFIA Animal Feed Division (AFD)*
The CFIA provides more information on the regulation of novel feeds at: http://www.inspection.gc.ca/animals/feeds/novel-feeds/eng/1370227088259/1370227136675

Definition of Novel Trait from the Feeds Regulations:

- "Novel trait," in respect of a feed, means a characteristic of the feed that

  (a) has been intentionally selected, created or introduced into the feed through a specific genetic change, and

  (b) based on valid scientific rationale, is not substantially equivalent, in terms of its specific use and safety both for the environment and for human and animal health, to any characteristic of a similar feed that is set out in Schedule IV or V.

Novelty determination guidance for feed is provided at:
http://www.inspection.gc.ca/animals/feeds/regulatory-guidance/rg-1/chapter-2/eng/1329298059609/1329298179464?chap=6#s25c6

- *Seeds Act and Regulations: CFIA Plant Biosafety Office (PBO) and Plant Biotechnology Risk Assessment Unit (PBRA)*
  These two groups work closely to manage the environmental release of plants with novel traits (PNTs). PBO is responsible for decision making surrounding novelty and authorizations of PNTs, and for establishing and implementing policy and programs for PNTs. PBO operates based on the science advice of the risk assessors in PBRA. For more information on the regulation of the environmental release of plants with novel traits, visit:
  http://www.inspection.gc.ca/plants/plants-with-novel-traits/eng/1300137887237/1300137939635

Definition of Novel Trait from the Seeds Regulations:

- "Novel trait," in respect of seed, means a characteristic of the seed that

  (a) has been intentionally selected, created or introduced into a distinct, stable population of cultivated seed of the same species through a specific genetic change, and

  (b) based on valid scientific rationale, is not substantially equivalent, in terms of its specific use and safety both for the environment and for human health, to any characteristic of a distinct, stable population of cultivated seed of the same species in Canada, having regard to weediness potential, gene flow, plant-pest potential, impact on non-target organisms and impact on biodiversity

To provide proponents with additional guidance on the determination of novelty, PBO provides Directive 2009-09: *Plants with novel traits regulated under Part V of the Seeds Regulations: Guidelines for determining when to notify the CFIA*
http://www.inspection.gc.ca/plants/plants-with-novel-traits/applicants/directive-2009-09/eng/1304466419931/1304466812439.

Regulatory Trigger: Special Cases

1) *A product does not trigger all three regulatory authorities:* Not all products will trigger regulation as novel foods, novel feeds, and for environmental release. For example, a herbicide-resistant turfgrass would not be expected to trigger regulation as a novel food if the turf species is not used as food. Similarly, a virus-resistant citrus cultivar would not be considered to be a PNT in Canada if the crop is not capable of surviving in this climate, even though approval for use as food and feed would still be required. When a novel product triggers the requirement for regulatory approval under more than one piece of legislation, Canada's "no split approvals" policy specifies that it will be authorized only once all implicated regulatory authorities are prepared to proceed.

2) *Retransformation/remutation:* It is noteworthy that, in certain cases, even if regulation is triggered, a full risk assessment may not be required by all three assessment groups (novel foods, novel feeds, and environmental release). One example of this is "retransformation." For the purposes of environmental release, retransformation is defined as the transformation of a plant with a DNA construct that has already been authorized in another variety of that species, provided that the intended uses are similar, and that the plant is known to be similar to the authorized PNT. (For more details, consult CFIA Directive 94-08.) A related policy applies to remutation events. This is particularly relevant to vegetatively propagated crops such as potato, with which incorporating a novel trait through conventional breeding methods is impractical.

In these cases, the plant is still considered to be novel, and is, therefore, subject to the same regulatory requirements as the original event. However, since a risk assessment would not be required, its authorization for environmental release could be greatly simplified. In principle, this concept would be equally applicable to some products of gene-editing technologies, although, with no formal policy in place at the time of this writing, consultation with regulatory authorities is encouraged early in the development process. Please note that, since Canada is a Codex signatory, Health Canada adheres to international guidance regarding recombinant-DNA technologies, and may, therefore, differ from the CFIA in decisions on whether assessment of retransformation events is required.

3) *A history of use in Canada:* Part V of the *Seeds Regulations* was drafted in such a manner that it grandfathered in potentially novel products of biotechnology that had already been released into the Canadian environment prior to its enactment. This means that, if a crop and trait were present in Canadian agriculture prior to 1996, it would not be considered to be a PNT. However, food or feed products derived from plants with an historic use exemption under the *Seeds Regulations* would not necessarily be exempt under the *Food and Drugs Regulations* or *Feeds Regulations*.

If this Part-V exemption had not been implemented, many products that fall within the "novel" category would have required assessment even though they may have already been safely grown for many years in Canada. Some examples of such products include triticale (released in Canada in 1969), canola (substantially equivalent to rapeseed), and triazine-tolerant canola (displaying novel herbicide tolerance).

Similarly, this concept of "new to Canada" continues to apply in novelty assessments. If a proponent can demonstrate that a trait was already present in that species in Canadian agriculture prior to 1996, then the trait is not novel for the purpose of environmental release. For example, if a plum cultivar with resistance to plum-pox virus had been cultivated in Canada prior to 1996, the genome of a different cultivar could be modified using gene-editing techniques to possess the same sequences and demonstrate the same resistance. Since the trait is not new to the species, a reasonable case could be made in some situations that this is not a PNT.

Pre-Submission Consultation

A pre-submission consultation is available to proponents who wish to discuss their products with regulators prior to making a submission. This consultation provides the proponent with an opportunity to present an overview of the submission and to ask specific questions regarding the content of the submission. Assessors will provide guidance on the information requirements specific to the individual product, explain regulatory requirements, and clarify expectations for data quality.

This practice often reduces the number of requests from regulators for either clarification or additional information that might otherwise have been required in order to complete a safety assessment and reach a decision. Health Canada and the CFIA have developed a guidance document for pre-submission consultation that is intended to provide new applicants with more information. It is available at:
http://www.inspection.gc.ca/plants/plants-with-novel-traits/applicants/pre-submission-consultation/eng/1368394145255/1368394206548.

Data Submission and Review

Where a safety assessment is required, the proponent must make applications to satisfy the data requirements of each regulatory group. In the case of novel foods, evaluators will perform a nutritional assessment and a toxicology assessment (which considers the chemical, toxicological, and allergenicity of the novel food) to determine whether the novel product is equivalent to its conventional counterpart, as well as a molecular characterization of the genetic change. The novel feed assessment includes nutrition, toxicology, and molecular reviews, but considers this information in the distinct context of use as feed. With respect to environmental safety, evaluators perform a molecular characterization, and assess the PNT against its conventional counterparts by reviewing information addressing: weediness, gene flow, plant-pest potential, impacts on non-target organisms, and impacts on biodiversity. There are many similarities in these reviews (for example, all three groups perform a molecular characterization); in recognition of this, evaluators are in regular communication with each other to maximize efficiency.

If, following a review of all submitted information, the evaluators have questions or require clarification of information submitted, a letter will be sent directly to the proponent outlining these questions and/or requests for clarification. Information requirements have been met when requests for further information and/or clarification have been satisfied. At this point, the science review is complete, and the regulatory decision will be made.

Regulatory Decision

When a plant is considered to be a PNT and a source of a novel food and/or a novel feed, regulatory decisions regarding the use as a novel feed, novel food and environmental release will be coordinated and harmonized to minimize the potential for unapproved products to enter the Canadian environment or food or feed supplies. Once regulatory decisions have been harmonized, the CFIA and Health Canada will send decision letters to the proponent and post a decision document on their respective websites. The decision document summarizes the information that was assessed, and the evaluators' findings.

Furthermore, risk management of certain PNTs may be required as a condition of authorization. Risk management imposes conditions on the use of the PNT such that identified potential risks to the environment are mitigated. Risk management may not be necessary or appropriate for all PNTs, but some (particularly insect-resistant and herbicide-tolerant PNTs) warrant a stewardship plan.

Considerations that may Impact Future Policy Development Relating to the Environmental Release of Products of Gene Editing

Advancements in molecular analysis techniques continue to contribute to our understanding of plant genomes and genetic change. Also, after nearly two decades with novel plant products available in the marketplace, a high degree of familiarity with these products has developed. In keeping with the comparative approach that Canada takes to assessing novel products, regulators from the CFIA and Health Canada undertook a literature review to compare the insertional effects that could arise during the creation of a PNT to other types of spontaneously occurring genetic changes in plants (Schnell *et al.*, 2014). The findings of this review will help to inform future policy direction, as the CFIA and Health Canada work towards ensuring that regulators are focusing their efforts on assessing novel products of biotechnology in a manner that is suited to the expected potential for risk.

The product-based approach to regulation allows the Canadian regulatory system to effectively adjust to any new developments in the science of plant breeding. Policy work is ongoing to help to ensure that guidance documents are available as products of gene editing are brought forward for assessment. The CFIA and Health Canada are committed to providing an efficient and appropriate level of regulatory oversight that encourages innovation while allowing Canadians to benefit from the advances brought by new technologies.

Reference

Schnell J *et al.* (2014) A comparative analysis of insertional effects in genetically engineered plants: Considerations for pre-market assessments. Transgenic Research 24(1) 1–17.

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DR. SHEARER particularly enjoys the aspects of her work that involve keeping policy relevant to rapidly-developing technology and knowledge.