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RESEARCH PAPERS

Canadian regulatory perspectives on genome engineered crops

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ABSTRACT. New breeding techniques in plant agriculture exploded upon the scene about two years ago, in 2014. While these innovative plant breeding techniques, soon to be led by CRISPR/Cas9, initially appear to hold tremendous promise for plant breeding, if not a revolution for the industry, the question of how the products of these technologies will be regulated is rapidly becoming a key aspect of the technology's future potential. Regulation of innovative technologies and products has always lagged that of the science, but in the past decade, regulatory systems in many jurisdictions have become gridlocked as they try to regulate genetically modified (GM) crops. This regulatory incapability to efficiently assess and approve innovative new agricultural products is particularly important for new plant breeding techniques as if these techniques are classified as genetically modified breeding techniques, then their acceptance and future will diminish considerably as they will be rejected by the European Union. Conversely, if the techniques are accepted as conventional plant breeding, then the future is blindingly bright. This article examines the international debate about the regulation of new plant breeding techniques and then assesses how the Canadian regulatory system has approached the regulation of these technologies through two more public product approvals, GM apples and GM potatoes, then discusses other crop variety approval and those in the regulatory pipeline.

KEYWORDS. biotechnology, gene editing, GM apples, GM potatoes, innovation, regulation, risk

1. INTRODUCTION

Science has historically functioned at a pace that is faster than that of regulatory agencies. As societies have becoming increasingly risk fixated, this problem has only been further compounded as regulatory decision timeframes for genetically modified (GM) crops have increased

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from six months in the late 1990s (Jaffe, 2005) to 65 months in 2011 (Phillips, 2011). A tenfold increase in the time it takes to receive regulatory approval for innovative crop varieties in the span of 15 years is more than troubling, it implies a grave threat to the future of plant breeding in both the developed and developing worlds. This is particularly the case when the majority of the GM varieties being approved still have the same basic traits of herbicide tolerance and insect resistance as did initial varieties. Given that these traits have been internationally regulated for over 20 years now, it is inconceivable that the time for regulatory approvals should have increased to the degree that they have. Especially when framed within the context that not a single safety concern for humans, animals or the environment has resulted from any regulatory agency risk assessment.

This deviation from science-based risk assessment in a timely and consistent manner can be traced back to the 2003 establishment of the European Food Safety Authority (EFSA). At this time, the European Commission decoupled the risk assessment process from the variety approval process. EFSA has the mandate and authority to undertake risk assessment of all new GM plant varieties and delivers upon this mandate relatively efficiently, albeit with a slight time lag to that of the Canadian and American regulatory agencies. The problem is that the European Commission is the body that determines which plant varieties are approved for commercial production within the EU and the committee that makes these decisions has become co-opted by the European environmental movement, resulting in a decade-long inability to function in any capacity. The European Commission decision-making body is the Standing Committee on the Food Chain and Animal Health and is comprised of one representative from each Member State (Smart et al., 2015, 2016). Often, this membership is held by officials from the government ministries such as the environment, rural affairs, consumer affairs or rural development. Rarely, is membership on this committee held by officials from the ministries of agriculture. European Union (EU) countries that are politically opposed to GM crops consistently vote against approval of new varieties, thus ensuring that no new GM crop varieties ever receive production approval within the EU.

While the EU has deviated away from science-based regulation, Canada has remained committed to the scientific principles laid down in its domestic regulatory framework for plants with novel traits (PNTs) 25 years ago. Canada's regulatory framework delivers timely and consistent approval decisions. While the approval of the initial product developed using gene silencing, GM apples in 2015, took considerably longer than approval for other GM varieties, the approval of GM potatoes (also developed using gene silencing) in 2016 occurred in a timely manner. As genomic engineering technology adoption increases at a rapid pace, it will be important to discern whether the approval process for either GM apples or GM potatoes has implications for the approval of crop varieties produced using these technologies. Approval efficiency is crucial to ensuring that regulatory uncertainty is as minimal as is possible, thus providing confidence for future research and development investments.

This article examines the regulatory approval process in Canada for new breeding techniques (NBTs) through summaries of the approval for GM apples, GM potatoes and other GM crops. The article is structured as follows. Section 2 provides the context to the regulation of NBTs. Section 3 offers detailed assessments on regulatory approvals for the products of NBTs. Section 4 offers some policy implications, with Section 5 providing a concise conclusion.

2. THE STATE OF NBT REGULATION

The discussions about how to best regulate NBTs began several years ago, about the end of the first decade of this century. Knowledge and understanding about genomic sciences advanced rapidly following the commercialization of the initial single trait varieties of GM canola, corn, cotton and soybeans during the 1995 to 1997 period. As the technology and capabilities progressed, stacked traits, with both herbicide tolerance and insect resistance, began to appear in the

early 2000s and by the end of decade numerous new breeding techniques were being applied.

As this knowledge and information began to be circulated within and between companies and then shared with regulatory agencies, resulting in discussions between the technology developers and regulators, a knowledge gap was identified in how to best regulate the new breeding techniques. In 2011, the Institute for Prospective Technologies and Society (IPTS) in Seville, Spain, held a workshop that examined some of the leading NBTs at this time (Lusser et al., 2011). This workshop covered some of the targeted mutagenesis techniques that had been developed and were being applied, such as oligonucleotide directed mutagenesis (ODM), zinc finger nuclease (ZFN), meganuclease technique and transcriptional activator like effector – nuclease (TALEN). Cisgenesis and intragenesis techniques were also included in the list of NBTs being discussed as was grafting on GM rootstock. Based on products in the pipeline this IPTS report expected that there could be as many as 125 new products in the marketplace by 2015.

As the products in the pipeline began to successfully emerge as approved products, particularly those developed by targeted mutagenesis, discussions began about the regulatory requirements and scrutiny for these new breeding techniques. Some simply raised discussion of how regulators would keep up with the rapid changes occurring within the field of genomic research (Waltz, 2012), while others expressed concerns about the level of regulatory scrutiny that was taking place as NBT products progressed through the regulatory system (Camacho et al., 2014; Whelan and Lema, 2015).

By early 2015, NBTs appeared on the radar screen of various European-based environmental groups. With nary a thought for the incredible potentials these technologies could offer in terms of new breeding opportunities to plant breeders and researchers in developing countries, not to mention the reduction in time and cost, these environmental non-governmental organizations (eNGOs) banded together to summarily dismiss all of these technologies (Panella et al., 2016). Leading the way were Greenpeace and Friends of the Earth, although the letter is signed by representatives of six additional eNGOs. This letter dictates to the European Commission that it must classify all of the new breeding techniques presently being utilized as genetically modified techniques and therefore be banned from use within the EU. Such a move would virtually end all plant breeding within the EU as targeted mutagenesis research technologies have been employed there for decades. The new dictum from the eNGO coalition would end up banning the majority of technologies that presently provide new crop varieties to European agriculture, which would result in higher taxes to pay the increased farm subsidies that would be needed due to European farmers lack of access to virtually any agriculture innovation.

The game changer in all of this, was the invention of clustered regularly interspaced short palindromic repeats (CRISPR, which is frequently referred to as CRISPR/Cas9) in 2012. (Ledford, 2015) Not only is the science revolutionizing the research world, the economics of it are equally as spectacular. The cost of single event transformations, while difficult to quantify, could have been as high as of a quarter of a million (Visser, 2016), however, the cost of genome editing could be as low as $30 (Ledford, 2015).

While the potential for plant breeding is boundless, the applicability of CRISPR/Cas9 in health genomic research also has great potential and it did not take long for controversy to explode when a group of Chinese scientists published a report in 2015 on their application of the technology to human embryos (Wang et al., 2015). While this application of gene editing technologies will undoubtedly be the subject of rigorous debate (both scientific and ethical) for the foreseeable future, in plant agriculture, the technology continued to advance, to the point that the first CRISPR-edited product was approved in the USA in early 2016 (Waltz, 2016). What was unique about this approval for the common white button mushroom is that the US Department of Agriculture (USDA) determined that gene editing technologies do not require regulation. To date, products developed by ZFN, TALEN and CRISPR have all reach the market with no regulatory oversight (Waltz, 2016). The USDA has determined that gene editing is the equivalent of conventional breeding in some instances and therefore do not

require regulatory oversight within the American regulatory framework. This decision not to regulate is based on the fact that no foreign DNA (transgene) was inserted through the application of the CRISPR/Cas9 gene editing change and that the change did not involve pesticidal properties, which would have automatically triggered review by the Environmental Protection Agency. The USDA perspective could perceivably change if transgenes or pesticidal properties were involved.

One jurisdiction that has developed a functional regulatory system for the approval of NBT products is Argentina. (Whelan, 2015) Beginning in 2012, regulators and policy-makes initiated discussions with the objective of providing greater clarity to plant variety developers regarding how products of NBTs would be regulated within Argentina's already developed GM regulatory framework. The resulting gene editing regulatory approach was developed to be consistent with the Cartagena Protocol on Biosafety (even though Argentina has not adopted the Protocol) and as a result, it is a flexible framework that relies on case-by-case assessment. Essentially Argentina's regulatory system identifies that if there is no new combination of genetic material and no transgenes have been used, the product is non-GM. If a transgene technology was used in the development of a product, where the final product is free of the transgene, this product is also classified as non-GM.

Once again, the world witnesses the rapid development of the trans-Atlantic gap that has plagued production of GM crops, that is, the EU rejects the technology entirely, while the Americas have embraced the technology. This 20 year battle has already cost the EU billions in terms of lost research funding as in the mid-1990s the EU received one-third of the global agriculture investment in research and development, which has now dropped to below 10% (Little, 2015).

3. CANADA'S EXPERIENCE WITH APPROVING GENOMICALLY ENGINEERED PRODUCTS

Canada's approach to gene editing technologies is no different from the technologies that have preceded it, in that if the technology creates a novel product, then Canada's PNT regulations are triggered, resulting in additional regulatory oversight on allergenicity, toxicity and impacts on non-target organisms. While no formal standard or definition for novel exists, Canadian plant breeders use a rule of thumb that if the specific trait they are selecting for expresses at 20% to 30% higher or lower than conventional varieties, the plant breeder initiates discussions with regulators regarding the applicability of PNT regulations in the specific instance. The PNT regulations apply to all plant varieties having a novel trait, regardless of how they were developed, meaning that the variety could be developed by gene editing, genetic modification, mutagenesis or even conventional breeding. It is expected that some of the gene editing technologies may create products that are PNTs, while some of them may create products that are not PNTs. Plant varieties that are subject to PNT regulations require unconfined release status from the Canadian Food Inspection Agency (CFIA) and Health Canada, prior to being registered as commercial varieties by the industry. This section will illustrate how Canada is regulating gene editing technologies through the examination of two recently approved technologies, apples and potatoes.

3.1. *Approved Gene Edited Products: Apples*

Apples produce polyphenol oxidase (PPO) when the flesh is exposed to air, resulting in the flesh turning brown. This process is known as oxidation. The novel solution developed by Okanagan Specialty Fruits (OSF) in British Columbia, Canada was to slightly change the gene responsible for production of PPO. OSF scientists were able to identify the genes responsible for oxidation in other apple varieties that expressed the oxidizing chemical at significantly lower levels and then down-regulate these genes in the apple variety they were working with, to create a non-browning apple. This technology was applied to develop non-browning varieties of Golden Delicious and Granny Smith apples.

These apple varieties were submitted to the American regulatory agencies in 2010 and to Canadian regulatory agencies in 2011. Approval in the US was granted in February 2015, with approval in Canada following one month later. US regulators took 5 years to assess and review the science and the apple itself. This is more than double the length of time it would normally take to review a submission for a plant variety approval. Normally, it takes between two and two-and-a-half years to undertake a risk assessment of a new plant variety. American regulators were exceptionally thorough in their assessment of this product, concluding that the Arctic varieties are similar to any other variety of apple, posing no risk to the environment or human health. Similarly in Canada, regulators took close to four years to approve the apple, which is nearly double the length of time required for other GM products.

This additional regulatory time for risk assessment can partially be justified in that this was the first GM apple to be submitted for variety approval, thus being a new plant species for the CFIA and Health Canada to apply PNT regulatory requirement to, as part of the risk assessment process. Scientists with Health Canada needed to ensure that the new varieties of Golden Delicious and Granny Smith apples were substantially equivalent to existing varieties already in the marketplace. While the safety of the varieties were assessed, so to was the nutritional value of the apples to ensure that the change in oxidation of the apple did not have an effect on nutritional values. Health Canada states that, "[s]cientists with expertise in molecular biology, microbiology, toxicology, chemistry and nutrition conducted a thorough analysis of the data and the protocols provided by the applicant to ensure the validity of the results" (Health Canada, 2016). Clearly, greater regulatory scrutiny was applied to the risk assessment of the first GM apple varieties given the lack of historical risk assessment of previous GM varieties of this species, such as would be the case with new varieties of GM canola, corn or soybeans.

Following this lengthy assessment, Health Canada concluded the following about their assessment of GM apples. "Following this assessment, it was determined that the changes made to the apple did not pose a greater risk to human health than apples currently available on the Canadian market. In addition, Health Canada also concluded that the Arctic apple would have no impact on allergies, and that there are no differences in the nutritional value of the Arctic apple compared to other traditional apple varieties available for consumption" (Health Canada, 2016). The product is able to enter the market with no additional regulatory compliance requirements, such as labelling. The developer, Okanagan Specialty Fruits, expects to have the first of its non-browning apples available for commercial sale by 2017.

3.2. *Approved Gene Edited Products: Potatoes*

The harvesting, storage and transportation of potatoes frequently results in the development of dark spots due to bruising on the vegetable, resulting in waste all along the supply chain. Simplot has developed a new variety of potato using RNAi technology that has identified the genes responsible for bruising and down regulated the genes responsible for dark spots. Simplot estimates that its new potato, the Innate potato, has reduced bruising by 44% (Simplot, 2016). This variety of potatoes also has lower expression of asparagine, decreasing the potential for the formation of acrylamide, a carcinogenic compound that occurs in potatoes when baked or fried at high temperatures. Studies done by Simplot estimate that acrylamide in Innate potatoes has been reduced by 52-78% (Simplot, 2016).

In the US, Simplot received approval for the first generation of Innate potato in 2014, with the approval for the second generation Innate potato coming in 2016. GM potatoes are available for sale in 11 grocery stores in the US southeast and Midwest. In Canada, Health Canada and the CFIA received the data submission dossier in 2015, providing approval for four varieties of Innate potatoes in May 2016. At present there are no GM potatoes available in grocery stores in Canada, although Simplot hopes to have products available for sale in Canada late in 2016.

This was not the first variety of GM potato to be submitted for risk assessment in either Canada or the US as Monsanto received approval for its Bt potato known as NewLeaf in 1995. This variety provided resistance predominantly to the Colorado potato beetle (Ryan and McHughen). While a substantial time period had passed between variety approval of NewLeaf potatoes and Innate potatoes, Simplot may have benefited from the groundwork established by Monsanto 20 years earlier. The timeframe for the risk assessment of this variety of GM potato was considerably shorter than that of apples, requiring slightly longer than 12 months to complete the assessment.

There is also a strong probability that Canadian regulators gained knowledge and insights from the more lengthy review timeframe for the GM apple varieties and were able to transfer this learning and risk assessment experience to their assessment of the GM potato varieties. Having adopted a diligent approach to the risk assessment of an NBT product designed for direct human consumption like apples, regulators within the CFIA and Health Canada will have documented safety and substantial equivalence data that would assist in the review of Simplot's potatoes.

3.3. *Products in the Gene Editing Pipeline*

New breeding techniques have been employed to develop new varieties of crops that have been submitted to Canadian regulators for risk assessment over the past few years. While it is still too early for CRISPR developed crops to have reached the stage where they have completed field trials and the requisite data has been gather to compile a regulatory submission package, they will be reaching this stage quickly. Once greenhouse variety lines have been assessed, selected lines are then put forth into field trials to gather agronomic data required to inform regulators. It typically takes three years of field trials to gather the pertinent information. Based on this, the first CRISPR-based varieties might have entered field trials at the very earliest 2016, however, 2017 or 2018 are more likely.

Other NBT technologies have been utilized and numerous varieties in several crop types have received approval in Canada. The earliest of these varieties were approved in 2012. Table 1 provides a summary of varieties approved that were developed based on NBT technologies. Five different crop types have successfully approved NBT varieties, with a total of 12 crop varieties having either been approved or are nearing the end of the approval process.

While the regulatory system has not been flooded with NBT submission, it has consistently received, assessed and approved these varieties. This is what the industry desires most of a regulatory system, the ability to deliver consistent decisions in a timely manner. The length of time to conduct the risk assessment on GM apples would appear to be an anomaly as crops that have a lengthy history of submitting and approving GM varieties would appear to have not experienced any noticeable delays in the approval process. As this was the first apple variety to fall under PNT guidelines, additional caution would appear to have been taken to satisfy regulators that GM apples are equivalent to every other apple variety presently available for commercial sale.

4. POLICY IMPLICATIONS

The pace of innovation is a rapid one, seemingly at times, incapable of slowing. The ability of science to advance so rapidly in terms of how to develop new crop varieties through scientific breakthroughs like CRISPR and other new breeding techniques, illustrates just how

TABLE 1. NBT approvals in Canada, 2012-2016.

Crop	2012	2013	2014	2015	2016*	Total
Alfalfa	1	0	0	0	0	1
Canola	0	1	1	0	0	2
Corn	0	0	2	1	2	5
Cotton	1	0	0	0	0	1
Soy	1	1	1	0	0	3
Total	3	2	4	1	2	12

Note*- These two varieties are still under review and have not been approved as of August 2016.

Source: http://www.inspection.gc.ca/plants/plants-with-novel-traits/approved-under-review/decision-documents/eng/1303704378026/1303704484236.

crucial it is for regulators to make efficient and timely decisions, but to ensure that risk assessments are thoroughly conducted. A difficult balance at times. Delays in regulatory approval have substantial investment impacts, where a regulatory delay of as little as one year for a public institution can reduce the return on investment by 20% (Smyth et al., forthcoming). Given that investment returns for public sectors are lower than that in the private sector, a 20% investment loss, could quite feasibly be the rational for not making an investment decision.

While the US regulatory agencies have publicly announced that products resulting from technologies such as CRISPR (provided no transgene or pesticial properties are involved), will not be regulated as a product of biotechnology (Waltz, 2016), but simply be treated as a product of conventional plant breeding, Canadian regulators have made no such pronouncement. Canada regulates based on the novelty of the trait, regardless of the breeding technology applied to develop the new variety. This means that conventional plant breeding mutagenesis, traditional biotechnology gene insertion or any of the new breeding techniques can result in a new variety that is defined as a PNT. However, it also means that if the variability of the trait is not outside of a range of 20% to 30%, then the new variety will not be a plant with a novel trait, but simply a new plant variety that would not be subject to the additional regulatory oversights of the PNT regulations. While the CFIA and Health Canada have not explicitly stated a trait range of 20-30%, conversations with plant breeders from various commodity types have indicated that if a trait expresses at more than 30% higher or lower then it would be expected to be treated as a PNT. Conversely, if the trait expresses at less than 20% then it would most likely not be classified as a PNT. Trait expression ranges of 20-30% require the developer to reach out and contact regulators to discuss the crop variety and trait. Based on conversations to date, plant breeders have indicated that following their discussions with regulators, crop varieties with traits expression changes in this range have thus far been treated as conventional varieties.

Where deviations from this could occur is when an entirely new plant species is submitted for risk assessment that has not previously been assessed as a PNT, such as was the case with GM apples. While it is technically the case that if a new breeding technology was applied to a crop that had not previously been breed using these techniques and the resulting product did not change the trait by more than 20%, it would not be classified as a PNT. However, plant breeders have regular communication with regulators about plant varieties that are in the research pipeline and that will be submitted for regulatory risk assessment and that in the course of these discussions, Health Canada and the CFIA may request that the submission be assessed as a PNT, even if this is not the case. The rational for this would be to ensure that from a physiological and environmental perspective that the new variety is substantially equivalent to existing varieties and as regulators, are acting to ensure that products entering the market are safe for human and animal consumption as well as the environment.

Canada's regulatory system appears to be well suited to regulating NBT products. The evidence to date is that products are entering the system, undergoing risk assessment and receiving approvals in an efficient period of time. What remains to be seen is whether Canadian regulatory agencies will follow the lead of American regulatory agencies and clearly state that some products of specific NBTs will not be treated as a product of biotechnology. A recent article by the CFIA observes, "[u]nlike regulatory frameworks that rely on specific processes to trigger regulatory oversight, or define what constitutes a GMO, the Canadian novelty approach encompasses new plant breeding technologies for the foreseeable future" (Macdonald, 2014).

5. CONCLUSIONS

While numerous regulatory agencies, particularly in Europe, are in a state of limbo regarding the regulation of products developed by NBTs, regulatory agencies in Canada have proceeded with the assessment and approval of such products. To date, Canadian regulators have assessed and approved ten different NBT

developed products, approving all of them for commercial production, with a further two presently under review. Clearly, Canada has established a science-based regulatory system that is flexible and capable of responding to new innovative products and technologies, without having to completely cease production approvals, such as is the case within the European Union.

Canada's approval of NBT products demonstrates that regulatory harmonization with the United States is important and that Canada's regulatory decision-making process delivers risk assessment decisions that are consistent with the USA. In the case of GM apples, Canada's approval followed that of US regulators by a few months. While the case of GM apple approval may be unique, given the time required for approval, the time for regulatory risk assessment was equal in both countries. Clearly, regulatory agencies in both countries undertook a thorough review of the science, the safety of the product and its potential impact on the environment prior to making their approval decisions. Based on these decisions, it would be expected that subsequent reviews of new GM apple varieties would be undertaken more expeditiously.

Science-based regulatory systems in both Canada and the USA, have proven their ability to safely and efficiently regulate the innovative products under development in agriculture. The precaution-based approach to new crop varieties, such as that utilized within the EU, demonstrates the challenges in trying to efficiently regulate innovative products. Canada has approved ten innovative NBT products over the past five years, while the EU has not approved an innovative crop variety in over a decade. Clearly, science-based approaches to the regulation of innovative crop varieties has been established (and proven) as the only means by which economical and environmentally beneficial technologies are able to reach the hands of farmers. Canada's record of NBT approvals to date demonstrates that the PNT system is capable of adjusting to new innovative products, something the EU regulatory system in not capable of demonstrating.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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