
The Canadian Regulatory Process for Plants with Novel Traits

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In this presentation, I will represent not only Plant Biosafety Office of the Canadian Food Inspection Agency (CFIA), but also Health Canada and the Animal Feed Division within the CFIA.

Canada differs from the United States in that it regulates novelty. We regulate novelty under three different acts applicable to three different groups: novel feed, novel food and novel plant assessments. The first is the *Seeds Act and Regulations*. The group that I represent—the Plant Biosafety Office—is responsible for the environmental authorization of plants with novel traits. A plant with a novel trait (PNT) is defined as:

...a plant into which a trait have been intentionally introduced and where the introduced trait is both new to cultivated populations of the species in Canada and has a potential to affect the specific use and safety of the plant with respect to the environment and human and animal health.

Under the *Food and Drugs Act and Regulations*, a novel food is defined as:

...a substance, including a microorganism, that does not have a history of safe use as food, 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.

My Health Canada counterparts often use the example of high-pressure processed ham as an example of a novel food because that's the process side, but products of novel plants are also considered novel foods. Under the *Feeds Act and Regulations*:

... only feed ingredients that have been approved and evaluated by the Animal Feed Division may be used in livestock feeds; approved ingredients are listed in Schedules IV and V of the Feeds Regulations. Any feed ingredient that is new (i.e. not listed in the Schedules) or has been modified such that it differs from conventional parameters, is required to undergo a premarket assessment. This concept applies to all novel feeds, including those derived through biotechnology.

Many entities, including microbial feed additives, are regulated under these feed regulations.

NOVELTY TRIGGERS

A PNT being assessed for unconfined release may also trigger a novel food/feed assessments by Health Canada and/or the Animal Feed Division of the Canadian Food Inspection Agency (CFIA).

A PNT is not necessarily a novel food or feed or *vice versa*. For example, genetically engineered turf grass is a PNT, but not a food or a feed. Genetically engineered timothy is a PNT, but not a novel food. And genetically engineered cotton is a novel food and feed, but not a novel plant—it does not trigger an environmental assessment—because it doesn't grow in the Canadian environment. Juice from genetically engineered citrus would only be a novel food because citrus trees don't grow in Canada and we would not expect anyone to import any citrus by-product as a feed. Therefore, the orange-juice people¹ have to deal only with Health Canada, whereas apple pumice is considered to be a feed ingredient, therefore Neal Carter² has had to go through the “feed” piece.

The basis for this is to ensure that an application is made only to the applicable group. If multiple applications are required, they should all be submitted at the same time to the applicable groups. After 2000, coordinated authorizations were ratified (Figure 1) whereby Health Canada and CFIA agreed to a no-split approval process. If multiple groups determine that a crop is novel, then the assessors work together to evaluate the product, and the authorization of the product is coordinated, usually within days of each other. This is done to minimize the potential for unapproved products to enter the Canadian food or feed supply.

To review: the Canadian process is unique. The focus is on the product, not on the process used to develop that product. Accordingly, a regulated product can be developed by any breeding process—including conventional breeding, genetic engineering or mutagenesis—and this approach allows the Canadian regulatory system to efficiently adjust to any new developments in science or plant breeding. Also, biotechnology is defined more broadly in Canada than in most other countries.

Figure 2 illustrates how the different groups come into play together under the mandatory premarket regulatory requirements for novel plant products. “Novel plant products” is the term that we use when referring to all three, but I'll use “plants with novel traits” (PNTs) because that is typically what we deal with.

¹Pages 75–85.

²Pages 87–94.

- Authorizations are co-ordinated under HC and CFIA’s “no split” approval policy (2000)
 - > Crops determined to be novel by the respective groups
 - > If multiple groups determine a crop to be novel then:
 - Assessors work together to evaluate the product
 - Authorization of the product is co-ordinated
 - > Used to minimize the potential for unapproved products to enter the Canadian environment, food or feed supplies.

Figure 1. Coordinated authorizations.

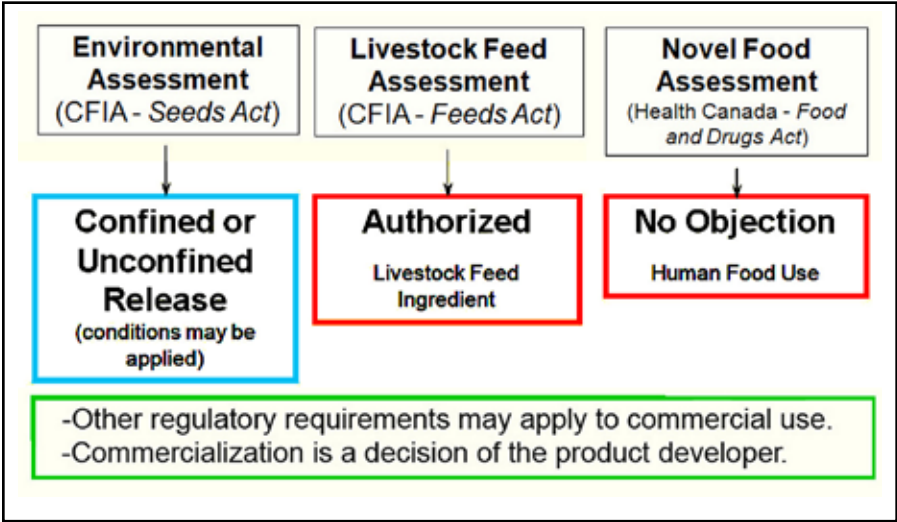
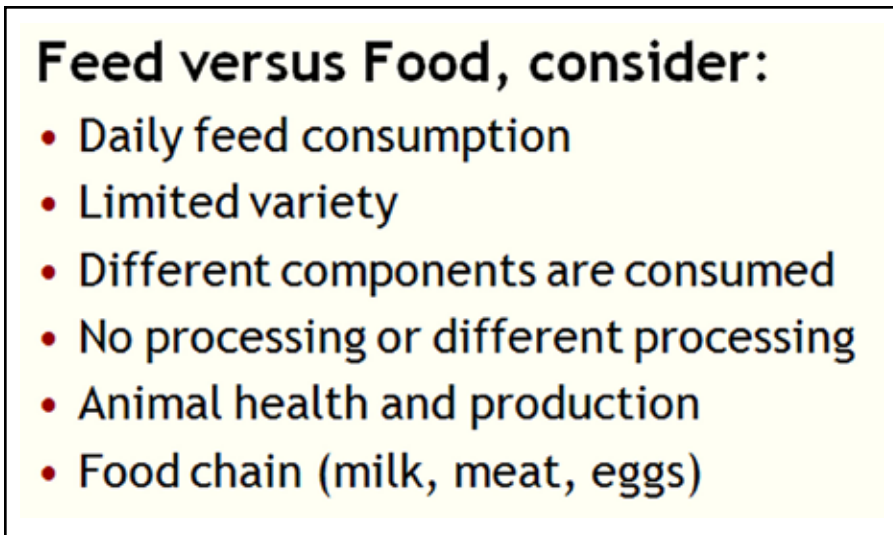


Figure 2. Mandatory pre-market regulatory requirements for novel plant products.

The environmental assessment is done by CFIA under the *Seeds Act*, with a confined or unconfined release. Confined release I’ll describe in more detail below. Unconfined release is when a product has been authorized for release into the environment and is considered as safe as its conventional counterparts. The livestock feed assessment is done by CFIA, based on the *Feeds Act*, when a product becomes authorized as livestock feed. The novel food assessment by Health Canada uses the terminology “no objection”; when they are done, they go through a food-ruling process and indicate a letter of no objection, which is posted on their web site. Other regulatory requirements may apply prior to commercial use. For instance, if the crop requires a variety of registrations in Canada, like soybeans or canola, then we have a variety of registration processes that must be completed prior to commercialization. And commercialization is always the decision of the developer.

FEED REGULATION

We are often asked why we regulate animal feed (Figure 3). Part of the reason is that, typically, the domestic animal's diet is made up of a small number of products at higher levels than we ever see in a human diet. Also, different components are consumed; humans may eat a different part of the plant from what animals eat, and no processing or different processing may be involved. Animal health and productivity impinge on the food chain and it is important that nutritional value or safety of products such as milk, meat and eggs are not affected. Assessments ensure that the feed is efficacious for its intended purpose and safe in terms of animal and human health.



Feed versus Food, consider:

- Daily feed consumption
- Limited variety
- Different components are consumed
- No processing or different processing
- Animal health and production
- Food chain (milk, meat, eggs)

Figure 3. Why regulate feed?

NOVELTY DETERMINATION

When it comes to novelty determination, it is the proponent's responsibility to characterize their plant and to self-identify to the CFIA a product requiring authorization for environmental release. We expect the developer to approach us and say, "I have a product that I think may be novel." Communication is key, and the earlier that communication takes place, the better.

The CFIA has the ultimate decision-making authority regarding regulatory status determination and reserves the right to require a proponent to provide scientific justification for determination that a plant is not a PNT. If we feel that it is and the proponent feels that it isn't, then the latter must provide justification in writing. Our assessment will be science-based and done on a case-by-case basis. Accordingly, this regulatory approach, again, is based on the product, not the process. Figure 4 shows essential questions to address whether a product is novel.

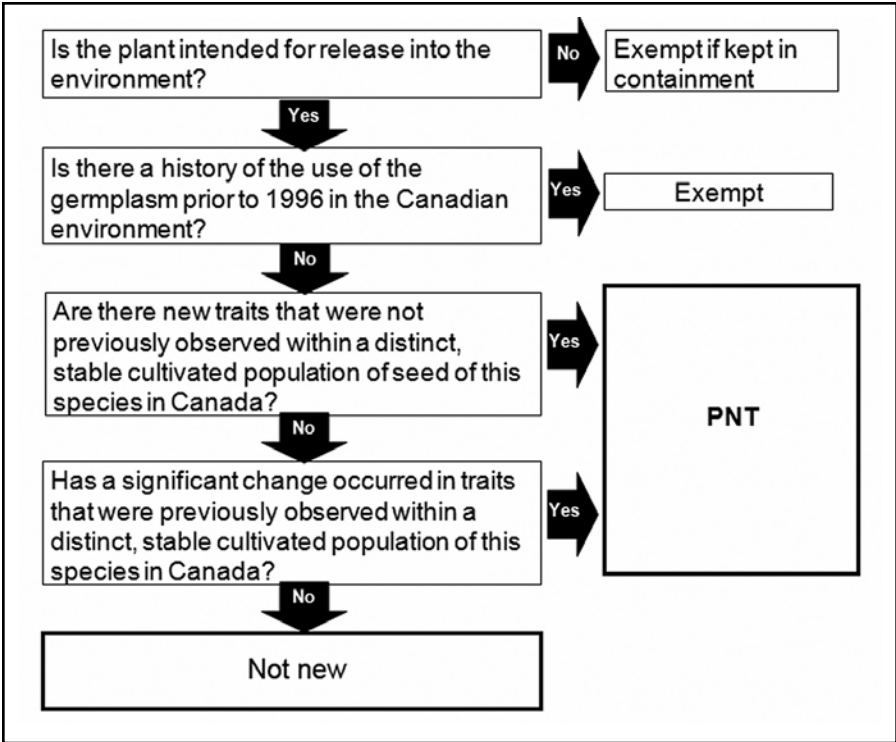


Figure 4. Regulatory approach: product not process.

Is the plant intended for release into the environment?

The CFIA does not have a regulatory requirement as long as the product is contained in a greenhouse, laboratory, etc.

If environmental release is intended, is there a history of use of the germplasm prior to 1996 (i.e. when the Seeds Act regulations came into effect for plants with novel traits)?

If the product was released into the environment prior to 1996, then, again, it is exempt from this process.

Are there new traits that were not previously observed within a distinct stable cultivated population of seed of this species in Canada?

This trigger may affect a conventionally bred product if it involves new germplasm containing a brand new, or very different, trait. For instance, in Canada, our list of regulated plant products includes a herbicide-tolerant wheat and a herbicide-tolerant sunflower, neither of which was developed through genetic engineering. Sometimes this causes us grief when people see “wheat” on the list, whereas wheat is not considered a living modi-

fied organism (LMO) and, therefore, in most countries is not regulated as a product of biotechnology. Because these wheat and sunflower genotypes each have a new trait, they become PNTs.

Has a significant change occurred in traits that were previously observed within a distinct stable cultivated population of this species in Canada?

If the answer is no, then it isn't new, but if it's yes, then it is a PNT.

When ascertained to be a plant with a novel trait, the next issue is whether it is of domestic or imported origin. If the latter, then an import permit policy has to be followed, on the application for which the PNT status is declared and it comes to my office—the Plant Biosafety Office (PBO)—for review. Once imported, if it is held in containment, then we would track that it stays in containment, whereas if it is to be tested in field trials, those trials would need prior approval. Along the left edge of Figure 5, “Ongoing communication with regulators,” signifies a critical aspect whereby we can help applicants to expedite the process.

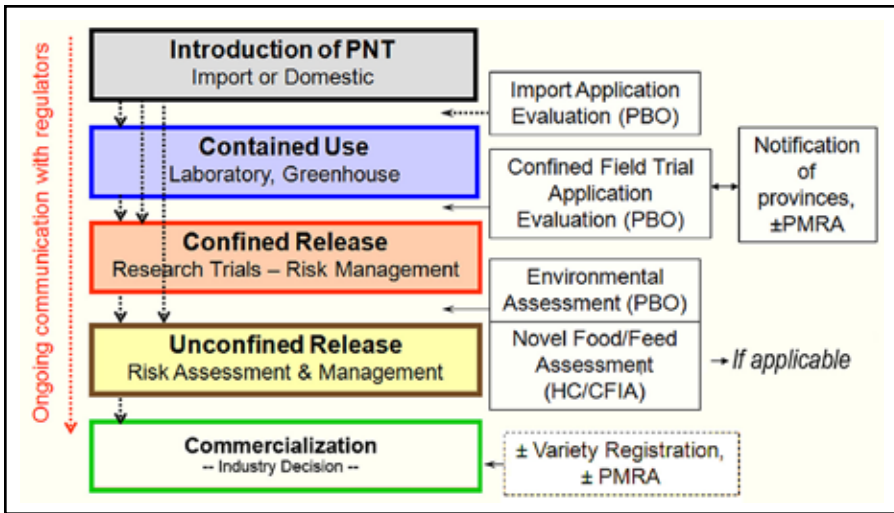


Figure 5. Regulatory pathways for PNTs.

Again, whether the PNT is imported or developed in Canada, if it stays in containment no further action is required. As soon as it is moved outside of the contained use into the confined release research trial program, then a confined field-trial application form must be submitted through the PBO, the purpose of which is to minimize risk by preventing entry into the animal and human food chains. When we receive a confined field-trial application, we notify the provinces, requesting comment in a minimum of 30 days. Therefore, our confined field-trial process takes at least 30 days. No deadline is stated on our website, but the earlier in the year that the application is received, the greater is the chance that the product will be approved for planting that year.

Many inspections are made under the confined release research program. Once the grower's data have been collected, the environmental assessment—the novel-feed, novel-food assessment piece—comes in, with the application for unconfined release, and from an environmental side, again, when unconfined release is authorized, we say that it's as safe as its conventional counterparts.

Again, commercialization is an industry decision, and if the PNT is a crop or a commodity that requires registration under the *Seeds Act*, then a variety of registrations must be completed before commercial sale of seed is possible.

ENVIRONMENTAL RELEASE OF PNTS

Risk equals hazard times exposure. A confined release is necessary when the environmental hazard is unknown or not fully characterized (Figure 6), *i.e.* the plant developer's research is ongoing, some of our questions are unanswered, and the regulatory program concentrates on environmental exposure and the evaluation and mitigation of risk.

• Risk = Hazard x Exposure

- **Confined Releases**
 - > Environmental hazard is unknown or not fully characterised
 - > Regulatory program concentrates on environmental exposure evaluation and mitigation
- **Unconfined releases**
 - > Environmental exposure of a known risk (maximum exposure is assumed)
 - > Regulatory program concentrates on environmental hazard evaluation* and stewardship, where required

*Sometimes referred to as “safety assessments” to distinguish them from quantitative risk assessments

Figure 6. Regulatory approach for environmental release of PNTs.

An unconfined release is possible when the risk is known and maximum exposure may be assumed; the regulatory program concentrates on evaluation of the environmental hazard, and we may introduce stewardship conditions that, sometimes, are referred to as “safety assessments” to distinguish them from risk assessments.

The purpose of our confined research field-trial program is to provide opportunities for plant developers to cultivate their PNTs in agronomic settings while minimizing environmental exposure. These trials are subject to conditions intended to minimize persistence and spread of the plant in the environment, and to prevent contamination of food and feed with unapproved plant material. Each trial is inspected multiple times by CFIA representatives to assess compliance with conditions, including post-harvest checks to determine that plant material has been adequately disposed of and to verify that it was produced exclusively for research purposes.

The purpose of the unconfined environmental-release program is to allow release of PNTs into the environment with limited or no restriction. It may require stewardship plans; for instance, prior to our authorizing a herbicide-tolerant crop, we require that the proponent tells us exactly how it will be managed and how development of resistance will be minimized. And for insect resistance, management requirements include refuges. The authorized products will have been assessed to be as safe as comparable products with a history of safe use. A question we ask is: “Does the addition of one or more traits change the plant’s impact on the environment in comparison to the same crop grown in the agricultural setting?” Once we have authorized a PNT, it is not handled any differently from its conventional counterparts.

We are often asked how many acres of genetically engineered crops are currently grown in Canada. It is approximately 99 percent of our canola and 97 percent of our corn, but the only way we can estimate acreage would be based on the adoption of the technologies in the various commodities.

REQUIRED SCIENTIFIC INFORMATION

Scientific information required in PNT applications includes:

- Identification and classification, comprising taxonomy, history of use and organism description
- Intended use of the PNT
- Description of the novel trait(s)
- Method used to detect the trait
- Molecular and agronomic data specific to the trait
- Optional: Participation in a public *Notice of Submission* initiative.

Regarding the optional item, the CFIA doesn’t have authority to have a mandatory comment period. We have what we call a “voluntary comment period,” in which most proponents participate. The invitation to make (a) comment(s) is a brief document—unlike what is posted in the United States—summarizing the data that we have received. We indicate that we will accept scientific comments, which only rarely are received, but the summary tells the public what we’re looking at and gives them the opportunity to tell us, typically, how opposed they are to genetically engineered technology in general.

ENVIRONMENTAL SAFETY ASSESSMENT

From an environmental perspective, we have what we consider the five main criteria or pillars of PNT environmental safety assessment; we look at the:

- Potential of the PNT to become a weed or invasive
- Potential for gene flow from the PNT to related species, the hybrid offspring of which may become a weed or be invasive
- Potential for the PNT to become a plant pest
- Potential impact of the PNT on non-target organisms
- Potential impact of the PNT on biodiversity.

Vis-à-vis the plant-pest criterion, the issue is whether the change in the plant makes it a potential sink for, say, fungal disease that could then impact neighboring crops. Regarding effects on non-target organisms, the main sources of concern expressed by members of the public are adverse effects on honeybees and monarch butterflies.

FOOD- AND FEED-SAFETY ASSESSMENTS

Regarding food and feed safety assessments, eight general considerations are applicable:

- A history of safe use
- Dietary exposure
- History of the organism(s)
- Characterization of the derived line in relation to the parental varieties
- Genetic modification
- Nutritional change
- Toxicology and allergenicity
- Chemical change.

More information on these factors is on our website.

ASSESSMENT PRINCIPLES

Essentially, we follow basic assessment principles (Figure 7), the first being tiering of data requirements, *i.e.* the degree of the scientific support required is adjusted based on the complexity, or our familiarity with, the product. Acknowledging that every product is unique, each has to be judged on a case-by-case basis. Products vary greatly in terms of their characteristics and no one set of prescribed data requirements is feasible. Certain

- **Tiering of data requirements:**
 - The degree of scientific support required is adjusted based on the complexity/familiarity of the product
- **Case-by-case**
 - Products can vary greatly in terms of their characteristics
 - No one set of prescribed data requirements is feasible
 - Data requirements are, instead, determined on the basis of the characteristics of the product in question
- **Familiarity:**
 - With particular products/characteristics
 - With assessing particular products/characteristics
- **Valid Scientific Rationale**
 - Can be used in place of data or to bridge data

Figure 7. Assessment principles.

considerations have to be addressed in every case, but again, each product is unique. Data requirements are determined on the basis of the characteristics of the product in question. Our familiarity with a particular product and its characteristics impacts the amount of information we require. A “valid scientific rationale” can be used in place of data or to bridge data. If it’s something that we have seen before, the proponent can present information from referee journals or the proponent’s own information to demonstrate that it’s the same as something that we’ve seen in a previous product.

A word of warning: we don’t like summary data. Companies that have submitted numerous dossiers to us sometimes include all kinds of summary data, which are not what we need. We need a rationale as to why we should look at the information we looked at with the prior product, which is much more acceptable than giving us copious summary data.

Other assessment principles are:

- The weight of evidence—the sum of the overall data submitted that provides the context for determining efficacy and safety
- Efficacy and safety side—the assessment considers the likelihood that unintended effects may be present in the modified plant in question
- Comparators must be appropriate for the product in question.

The last of these principles is included because often we receive submissions that refer to submission to the US Environmental Protection Agency, for example. When submitting for a product in Canada, relevance to Canada is preeminently important. For instance, for corn rootworm products in Canada, the corn-production system frequently includes crop rotations and other differing factors, which should be included in the story. Providing us with information on how a product is used in the US environment can complicate our assessment instead of making it easier.

DECISION MAKING AND POST AUTHORIZATION

While a file is under review, we often ask for more information to provide clarification. When all of our questions are answered, we may “flat-out” authorize a product. Or, we may authorize it with conditions, such as stewardship requirements. Some companies are now indicating to us that they never planned for a product to be marketed alone, that it would always be combined with another product. Accordingly, sometimes our conditions now reflect the fact that a product is authorized for combination with another, which affects the stewardship conditions that we will put in place. Of course, authorization may be denied. On the other hand, we’ve had files withdrawn, we’ve had files for which we have asked questions and are still waiting for answers, but CFIA has never refused an authorization.

We do not provide split—food/feed/environment—approvals. Separate decisions are posted on both the CFIA and the Health Canada websites. The applicant is required to notify CFIA and Health Canada immediately if new information on the plant becomes available, a condition always included in our authorization letter.

Compliance monitoring of conditions of authorization by the CFIA is ongoing. For instance, with *Bt* corn, resistance-management programs are in place which we actively

monitor to determine levels of compliance. Also, we work with Crop Life Canada to monitor levels of compliance from their perspective.

Stacked events constitute a special case. After a PNT has been authorized for use by the CFIA, the plant can then be traditionally bred into new varieties. However, if two or more events are combined, PBO must be notified prior to intentional release, so that we may ensure that the conditions of authorization of the individual plant lines are compatible and that a “stack” isn’t likely to create a problem. PBO must notify the proponent within 60 days of any concerns regarding unconfined environmental release of a “stack.”

IN SUMMARY

Canada’s regulations are product-based, not process-based. We have authority within the regulations for departments to approve products derived from biotechnology after the completion of the required safety reviews, and—once authorized—products of biotechnology are not treated differently from other foods, feeds or crops.

Applicants should plan for 24 months or more from submission to authorization. Ideally, less time will be required, but, especially, if we are dealing with a product type that we haven’t seen before, allowance of more time is recommended. We have biology documents that become part of our assessment, so if you know we’re going to be seeing something completely new, the more advance notice we can be given, the better.

More information may be accessed via the website URLs shown in Figure 8. For novel foods, it’s Health Canada. For novel feeds, it’s the Animal Feed Division of CFIA. Plants with novel traits is the CFIA, and there’s a CFIA Agricultural Biotechnology site for direction to various other pieces.

Talk to the regulators early and often. That’s what we’re here for and we want the process to progress as smoothly as possible for you. Again, avoid US-centric submissions.

<p><u>Novel Foods</u> Health Canada Web address: http://www.hc-sc.gc.ca</p> <p>HC-Novel Foods Web address: http://www.novelfoods.gc.ca</p> <p><u>Novel Feeds</u> Animal Feed Division address: http://www.inspection.gc.ca/animals/feeds/eng/1299157225486/1320536661238</p>	<p><u>Plants With Novel Traits</u> CFIA Web address: http://www.inspection.gc.ca</p> <p>CFIA-Agricultural Biotechnology Web address: http://www.inspection.gc.ca/english/sci/biotech/biotech_e.shtml</p>
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Figure 8. For information concerning novel foods and plants with novel traits in Canada.



PATRICIA MCALLISTER is the acting national manager of the Plant Biosafety Office (PBO) at the Canadian Food Inspection Agency (CFIA) in Ottawa. The PBO is responsible for the confined field-trial program and the authorization for environmental release of plants with novel traits.

Ms. McAllister was born and raised on a farm in New Brunswick that produced seed potatoes, vegetable crops and beef cattle. She received her Bachelor's degree in horticulture and a Master's degree in food science from the University of Guelph. She joined Alberta Agriculture and Rural Development as a seed-potato specialist in 1997, and has been with the CFIA since 2009.