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Molecular farming- importance of stewarding food crops engineered to produce transferred food allergens and non-food substances

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Developers are looking for new ways to produce proteins and other substances for food, pharmaceutical and industrial use by genetically engineering food crops to produce the desired substance of interest (i.e., molecular farming). Developers should be aware of the food safety concerns, legality and potential liability, and loss of consumer confidence that could arise if food or other plant materials from these crops were to inadvertently enter the food supply and compromise safety. At the earliest stages of product development, developers should consider whether it is feasible to consistently steward their crops and resulting plant materials from development through disposal to ensure they do not enter the food or feed supply in a way that would be unlawful. Developers should engage FDA's foods program when considering their stewardship program. While molecular farming holds promise for the economical production of specific proteins and other substances at a large scale, it is important for developers to consider the efforts needed to protect the food supply from the crops used for molecular farming- particularly when the crop chosen for molecular farming is a crop traditionally used for human or animal food.

KEYWORDS

Biotechnology, molecular farming, food safety, food allergen, pharmaceutical, stewardship

1 Introduction

In today's innovative environment, developers are looking for new ways to produce proteins and other substances for food,[1] pharmaceutical and industrial use. Some developers may look to produce these substances in food crops by genetically engineering the crop to produce a specific substance of interest. For example, some developers are interested in using plants to produce proteins commonly found in animal products as an alternative to animal agriculture (Wolf, 2023). As another example, innovators may wish to produce pharmaceutical or industrial substances in food crops to enable large-scale production (Vianna et al., 2011; Fischer and Buyel, 2020; Gerszberg and Hnatuszko-Konka, 2022; Long et al., 2022). After

1 "Food" refers to food for humans as well as food for animals.

harvest, the desired substance is purified from the crop and enters its intended commercial supply chain. This production process is generally referred to as "molecular farming." The concept of molecular farming is not new (Food and Drug Administration, 2002; Pew Initiative on Food and Biotechnology, 2002), but it is seeing renewed interest in producing valuable proteins on a large scale (Vianna et al., 2011; Fischer and Buyel, 2020; Gerszberg and Hnatuszko-Konka, 2022; Long et al., 2022). Practiced carefully, molecular farming could enable lower-cost production methods for high-value products.

While molecular farming holds promise for economical production of specific substances at a large scale, it is important for developers to consider the efforts needed to protect the food supply from the crops used for molecular farming- particularly when the crop chosen for molecular farming is a crop traditionally used for human or animal food.[2] These new types of plant varieties (and their resulting products) need to be stewarded such that they do not become food safety hazards in the food supply. Firms using food crops in molecular farming applications should consult FDA's foods program when considering the steps necessary to ensure material from their crop does not intermingle with conventional crops and inadvertently enter the food supply in a way that would be illegal (e.g., presence in the food supply of food containing an unlabeled major food allergen).[3] This article is intended to raise awareness of the food safety considerations that may be associated with "molecular farming," and will present FDA's experience with cases and consequences of inadvertent commingling.

2 Production of non-food substances in food crops

Some developers may be using food crops to produce non-food substances such as pharmaceuticals or industrial proteins. Developers should be aware of the food safety concerns, illegality, loss of consumer confidence and potential impacts on food availability that could arise if material from these crops were to inadvertently enter the food supply in an unlawful manner. The presence of a pharmaceutical or industrial substance could adulterate the food, present a safety hazard, and damage confidence in the integrity of the food supply. Such adulterated food could result in regulatory action by FDA such as product seizure and/or recalls.

The concerns around pharmaceutical-producing crops inadvertently being present in food are not new. The interest in molecular farming in the early 2000s raised concerns about the risk such crops might pose to the food supply. More than 10 years ago broad concern was expressed that pharmaceutical-producing crops would contaminate food crops through cross-pollination or through physical mixing of seed during crop production and processing. Murphy (2007) explained, "In the current atmosphere of heightened concerns over food safety and biosecurity, the future of biopharming may be largely determined by the extent to which the sector is able to maintain public confidence via a more considered approach to containment and security of its plant production systems." One paper (Rissler and Stillerman, 2008) explained that a contamination incident could cause detrimental health effects in humans and animals[4] and put food companies at risk for market losses, legal liability, and brand damage.

In 2004, the National Research Council (NRC) said, "Alternative nonfood host organisms should be sought for genes that code for transgenic products that need to be kept out of the food supply" (National Research Council, 2004). The NRC further explained, "An organism that is typically grown to produce a common and widespread food product probably would be a poor choice as a precursor for an industrial compound unless that organism were to be grown under stringent conditions of confinement. This is an important issue for any novel compound or GEO [genetically engineered organism] for which zero tolerance of bioconfinement failure is needed. Engineering organisms that are not otherwise used for food or feed could be an effective way to prevent a transgenic compound from entering the human food chain."

The Pew Initiative on Food and Biotechnology; FDA; and the Cooperative State Research, Education and Extension Service of the United States Department of Agriculture (USDA) held a workshop in 2002 where they explored several issues regarding the production of pharmaceuticals in food crops (Pew Initiative on Food and Biotechnology, 2002). The workshop discussion showed that food producers had concerns about the impact of a pharmaceutical-producing crop entering the food supply and its potential to cause illness, injury, product recalls, lasting damage to brand names, and international market disruption. Food producer concerns might be summed up in a quote from a representative of the National Food Processors Association, "I would strongly recommend and strongly expect that any industry, any group that's pursuing this to get it right the first time and to get it right every time".

This history could prove useful as firms look to move forward with molecular farming. There is a robust collection of literature from the early 2000s discussing molecular farming and the relevant safety concerns. For example, Murphy (2007) discusses some of the

2 Use of a non-food crop for production would seem to largely mitigate this concern.

3 Questions related to the safety of food for humans may be addressed to the Office of Food Additive Safety in FDA's Center for Food Safety and Applied Nutrition at plantbiotech@fda.hhs.gov.

4 While much of the attention has focused on food for humans, similar issues exist for food for animals. While the animal food supply could, in general, be subject to many of the same concerns expressed for the human food supply, there are additional considerations with respect to the safety of animal food. Animal food derived from a single crop-type may constitute a significant portion of an animal's diet. Therefore, a change in the level of a nutrient or the presence of a new substance even at low levels, may have a significant impact on the health of an animal, given a high level of exposure. In addition, nutrient composition and availability of nutrients are important safety considerations for animal health. Finally, animals consume plants, plant parts and plant byproducts not consumed by humans. It is important for developers of new plant varieties developed for nontraditional uses to recognize that their new plant varieties may raise safety or legal concerns when used in animal food. If developers have questions about the safety or legality of a new ingredient in animal food, including those derived from new plant varieties, they can contact FDA's Center for Veterinary Medicine's Division of Animal Food Ingredients in the Office of Surveillance and Compliance.

challenges of molecular farming in commodity food crops. While technologies and protocols around confinement have advanced since these reports were published (Clark and Maselko, 2020; Klocko, 2022), these reports still offer an important perspective. Even with advances in technology, some of the historic challenges associated with molecular farming, such as the possibility of human errors, remain and may cause a loss of trust in the safety of the food supply that consumers depend on each day.

3 Food allergens are a food safety concern

In the 1990s, a company transferred a gene from a major food allergen into a crop plant, a gene for a Brazil nut protein into a soy variety to improve its nutritional profile for animal feed (Nordlee et al., 1996). Upon discovery that the transferred Brazil nut protein was an allergen, the developers voluntarily discontinued development of the new variety because of the food safety risk to individuals allergic to Brazil nuts. The developers were concerned that they could not ensure that the modified soybean would not inadvertently get into human food, even though they intended it only for use in animal feed.

Recently, some developers have proposed producing animal proteins in plants. In some cases, the animal proteins may be known food allergens. In such cases, the plant would produce a food allergen that has never before been associated with it. Allergic individuals would not expect a plant food to contain an allergen from an animal. Consequently, it is very important that such crops are stewarded in a manner that protects allergic consumers. In April 2023, the Food and Drug Administration (FDA) issued an industry-wide letter describing considerations developers should take into account when transferring known allergens into new food crops (Food and Drug Administration, 2023). Adverse reactions to food allergens can be severe or even life-threatening–even when the allergen is present at low levels. Identifying and avoiding food allergens is the most effective way for consumers with food allergies to prevent allergic reactions. For example, consumers allergic to a protein in milk will read the label of packaged multi-ingredient foods and avoid those that list milk as an ingredient. However, if milk-protein-producing soybeans were inadvertently commingled with commodity soybeans, a vast array of soy-containing food products could suddenly be potential carriers of the milk allergen, with no way for consumers to identify and avoid such food products.

4 Enforcement actions related to pharmaceutical and industrial substances

The challenges associated with stewarding a plant producing a pharmaceutical or industrial substance are not a new concern. Some field trials of pharmaceutical-producing crops have resulted in enforcement action by USDA's Animal and Plant Health Inspection Service (APHIS) because the developer did not follow containment or confinement requirements (APHIS, 2020). In 2002, APHIS inspectors found volunteer corn (corn that had newly sprouted from the preceding year's planting) growing within a soybean field that had been a field test site for a pharmaceutical-producing plant in the previous season. Commercial corn surrounded the site within the isolation distance. The developer failed to notify APHIS of volunteers with tassels within 24 h of discovery. As a remedial measure, the developer was required to destroy all corn seed and plant material within 1,320 feet of the previous year's test plot. APHIS inspectors supervised the destruction of the regulated corn seed and plant material.

That same year, at a second location operated by the same firm, APHIS found volunteer corn from the previous year's test growing in a soybean field.[5] The firm was required to remove the volunteer corn to prevent it from being harvested along with the soybeans. After APHIS informed the grower that the volunteer corn had to be removed, the soybeans were harvested along with the volunteer corn plants in the field. The harvested soybeans potentially containing material from the volunteer corn plants were then sent to a storage facility where they were mixed with 500,000 bushels of soybeans. As a remedial measure, APHIS and the company stopped the movement of the soybeans at the storage facility and ultimately destroyed the 500,000 bushels of soybeans. The firm paid a $250,000 penalty and agreed to reimburse USDA for destroying the soybeans (see APHIS, 2020 for details). During Congressional testimony in 2003, FDA Deputy Commissioner Lester Crawford explained, "Although the amount of genetically engineered material commingled with such a large amount of soybeans was very small and FDA was confident that there was no health risk, the material should not have been present in the soybeans. FDA, USDA and the State of Nebraska have ensured that these soybeans will not enter the human or animal food supply," (Crawford, 2003).

In the cases that have occurred to date, APHIS and the developers have taken remedial actions to protect agriculture, the food supply, and the environment. Fortunately, no adverse effects to human or animal health were associated with these incidents. Nevertheless, the presence of non-food substances in the food supply could result in a robust enforcement action by FDA and a significant industry response affecting many components of the food system.

5 Stewardship

At the earliest stages of product development, developers should consider whether it is feasible to consistently steward their crops and resulting materials to ensure they do not enter the food supply in a way that would be unlawful. Special procedures will be necessary to ensure adequate stewardship of these crops. Such stewardship could include steps during seed production, planting, harvest and storage on the farm; transport; processing and formulation to make sure that all potential risks of exposure (e.g., inadvertent commingling) are addressed in a manner that protects

5 As a result of these incidents APHIS increased the isolation distance requirements and other conditions associated with field tests of plants engineered to produce pharmaceutical and industrial compounds and increased the number of inspections associated with these field tests (APHIS, 2003).

FIGURE 1
These piles of cottonseed are commingled with cottonseed containing an unauthorized plant incorporated protectant (PIP) due to human error in 2008. Approximately two-tenths of an acre of research cotton expressing an unauthorized PIP was inadvertently harvested with a 54-acre commercial cotton field. Both piles of cottonseed were held in place for several months until the regulatory violations were resolved. In commodity handling systems that gather products from numerous sources, even small amounts of unlawful material can affect a significant amount of product. Photo courtesy of FDA.

consumers by ensuring food safety. Past instances of inadequate crop stewardship have often been a result of human error (e.g., harvesting the wrong field see Figure 1), failure to follow specific protocols (APHIS, 2020), so it is critical that stewardship procedures address the potential for human error.

Closed-loop (identity-preserved) production systems have been successfully used for the production of certain specialty crops with quality enhancements and may provide useful experience and insight into stewardship considerations (Elbehri, 2007). Importantly, however, the fact that closed-loop preservation and segregation systems have been successful for use with some products may not necessarily mean the same system will be able to meet the stringent requirements necessary for preserving and segregating materials containing food allergens, pharmaceuticals or industrial substances. For example, closed-loop systems intended to preserve and segregate oilseeds with modified fatty acid composition to maintain a quality specification may need to be strengthened when the intent is not merely to preserve product quality but to ensure food safety.

6 Lessons from StarLink corn

Past experiences highlight some of the difficulties that can arise when products are not properly stewarded. A well-known example occurred in the early 2000s when StarLink corn containing the pesticidal protein Cry9C was found in taco shells intended for use as human food. The presence of Cry9C in human food is illegal because it is a pesticide that EPA has not authorized for use in human food due to concerns about potential allergenicity; however, EPA did authorize its use in animal food (Environmental Protection Agency, 2008) and USDA granted it non-regulated status with respect to plant pest issues. StarLink corn was planted for animal food use and became commingled with corn used for human food resulting in the human food containing Cry9C-an unlawful pesticide chemical residue in human food. FDA is responsible for enforcing pesticide chemical residue violations in food. FDA recommended testing for the presence of Cry9C protein in shipments of yellow corn and dry-milled yellow corn. Companies recalled human food products containing Cry9C. FDA also received adverse event reports associated with Cry9C-containing foods, although a subsequent study by the Centers for Disease Control and Prevention (2001) did not find evidence that Cry9C was responsible for the adverse events reported. Testing of yellow corn continued until 2008, when an EPA analysis indicated that StarLink corn had been sufficiently removed from the food supply such that the testing recommended by FDA was no longer necessary. Data available to EPA indicate that 4 million tests were performed on 4 billion bushels of corn. StarLink corn was planted on about 600,000 acres over the course of 3 years which represented less than half a percent of the total acreage planted to corn in the United States.

StarLink corn resulted in the recall of food products, lawsuits, Congressional hearings and damage to brands and reputations. A first-hand account by an executive from the company that produced StarLink corn explained, "It was a big deal, I got death threats. More than 300 food products were recalled. Containment efforts required 200 people." The incident resulted in, "a sharp decline in corn exports to major trading partners." "Ships literally turned around and were told to dump their corn into the sea" (Maurer, 2020).

While StarLink corn did not express a pharmaceutical, industrial or known allergenic substance, the lengths to which the food industry and governments went in responding to this incident are noteworthy, particularly considering that the presence of Cry9C in food for humans, although illegal, was not found to cause harm to health. Depending on the circumstances, a known food allergen, pharmaceutical, or industrial substance inadvertently present in the food supply could result in a response of even greater scale, effort and cost.

7 Overall considerations from farm to consumer

Molecular farming approaches may have promise in producing valuable proteins for use as food ingredients, pharmaceuticals or industrial substances. Developers and manufacturers considering molecular farming techniques should fully consider the potential food safety and other legal issues that may arise if their products enter the food supply in an illegal or unsafe way. Considerations might include establishing and maintaining conditions throughout the supply chain to ensure that material from the plant does not enter the food supply in an illegal manner. As a general matter, firms should take steps to keep material not intended for food use out of the food supply. If it does not seem feasible to take all the steps necessary to adequately safeguard the food supply, it may be prudent to reconsider product development plans. Failure to consider these issues and take appropriate action could result in severe health risks for consumers and undermine public confidence in using innovative technologies to make food,

pharmaceuticals, and industrial substances. At the same time, there may be innovative strategies to address some of the challenges described here. FDA encourages firms to consult with the agency on food safety issues early in the development process as they innovate in this area with an eye toward advancing production platforms that protect the food supply (see text footnote 3).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

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