

Assessing FDA Pathways For Genome-Edited Plant Foods

By **Emily Marden and Diane McEnroe** (March 21, 2024)

In February, the U.S. Food and Drug Administration clarified the regulatory pathway for foods produced from genome-edited plants in the form of a final guidance issued by the agency's Center for Food Safety and Applied Nutrition and Center for Veterinary Medicine, titled "Foods Derived from Plants Produced Using Genome Editing."

The guidance, which came seven years after the FDA invited public comment on the subject, addresses the regulatory approach for both human and animal foods produced from genome-edited plants.

In so doing, the guidance makes clear that there are two available routes for foods from genome-edited plants, including a streamlined premarket meeting option, based on the type of edits and associated FDA safety concerns.

In this sense, the guidance is consistent with the 2017 update to the Coordinated Framework for the Regulation of Biotechnology, as well as the Biden administration's 2022 Executive Order No. 14081 on advancing biotechnology and biomanufacturing innovation, which included a promise to clarify — and potentially simplify — regulatory pathways for products of biotechnology.

The guidance is timely because genome editing has become the dominant tool for targeted modification of plants to produce desired traits and novel proteins for both human and animal use. The FDA defines genome editing in this context as "methods that can be used to produce new plant varieties by creating genetic changes at specific sites in the plant genome," which includes but is not limited to CRISPR and TALENs.

The guidance may also have significance for those developing novel human foods more broadly. It provides an up-to-date list of the FDA's key safety concerns regarding novel ingredients that will be useful in considering the path to market for novel ingredients produced using genome editing in microorganisms as well as more traditionally genetically engineered plants.

In addition, the guidance introduces a streamlined path to market for lower-risk novel foods, which may provide opportunity for other foods and food ingredients currently subject to voluntary notification programs to explore.

Two Regulatory Pathways Available for Foods Produced From Genome-Edited Plants

The FDA has expansive regulatory authority under the Federal Food, Drug, and Cosmetic Act to ensure human and animal food is safe and properly labeled.

Under the Coordinated Framework for the Regulation of Biotechnology developed in 1986, the FDA shares jurisdiction over products derived from biotechnology with the U.S. Department of Agriculture and the U.S. Environmental Protection Agency.[1]



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The coordinated framework seeks to strike a balance between regulation that protects public health and the environment, while maintaining flexibility to avoid impeding innovation.

It considers biotechnology to be an extension of traditional methods of production, and concludes that existing laws administered by these federal agencies are adequate to provide regulatory oversight based upon product uses.

As such, regulatory authority is distributed among these agencies depending on the nature of the product, which often results in overlapping — and evolving — regulatory requirements for products relying on genome editing.

The coordinated framework was updated in 2017 in an effort "to increase public confidence in the regulatory system and to prevent unnecessary barriers to future innovation and competitiveness."

Historically, the vast majority of foods reviewed by the FDA under the coordinated framework have been derived from genetically engineered plants and microorganisms pursuant to its 1992 "Statement of Policy: Foods Derived from New Plant Varieties."

The new plant variety policy directs developers of such products to submit a robust safety assessment for FDA review.

In 2017, the FDA asked for stakeholder input on the appropriate approach to evaluate the safety of foods derived from genome-edited plants, including whether there are specific risks that should be considered and whether there are categories of products that may pose less risk than others. The FDA issued its recent guidance in response to this request, and after reviewing the reported 580 comments that the agency received.

Fundamentally, the guidance confirms that the FDA's new plant variety policy premarket consultation also applies to human and animal foods from genome-edited plants.

At the same time, the guidance represents a sharp change from the new plant variety policy because it introduces a second voluntary premarket notification pathway specifically for foods from genome-edited plants, a so-called premarket meeting, which requires less information and which may provide less industry and consumer comfort than what is required for a premarket consultation offered under the new plant variety policy.

The net result is that developers of foods from genome-edited plants are encouraged to engage with the FDA either through a premarket consultation, as outlined in the new plant variety policy and currently conducted by the FDA, or through the newly introduced premarket meeting pathway.

Both of these pathways are voluntary, and the FDA strongly encourages engagement "to help identify the data and information most relevant to food safety or other concerns specific to food from the new variety" and to provide the FDA "with an awareness of the genome-edited plant products potentially on the market."

The FDA also makes clear that the allergen labeling requirements for all foods under the Food Allergen Labeling and Consumer Protection Act of 2004, which were enacted after the new plant variety policy, must be met.

The FDA's move to streamline pathways to market differs somewhat from the U.S.

Department of Agriculture's Animal and Plant Health Inspection Service efforts to do the same with implementation of the 2020 Sustainable, Ecological, Consistent, Uniform, Responsible, Efficient Rule.

Similar to the guidance, the SECURE Rule takes a streamlined risk-based approach. However, to do so, the SECURE Rule exempts plants containing certain low-risk genetic modifications from any permit requirement; in such cases, the developer can introduce the plant without notifying APHIS.

In contrast, while the FDA also aims to streamline its regulatory approach for foods produced from genome-edited plants, it urges developers to notify the agency — through either a premarket consultation or meeting — that it plans to introduce food from a genome-edited plant. The FDA explains in its guidance that such transparency helps to "foster public confidence and transparency in the use of such technologies."

The pathway choice is risk-based: If the food from a genome-edited plant introduces certain traits or changes, the FDA encourages a voluntary premarket consultation, while, if the food from a genome-edited plant does not raise safety risks, the FDA recommends a premarket meeting. In this sense, the guidance reflects an up-to-date view of the FDA's safety concerns.

Premarket Consultation

More than 30 years after instituting the new plant variety policy, it appears that the FDA has crystallized its key safety concerns regarding this category of products.

Thus, even while noting that the vast majority of new plant varieties only very rarely raise safety issues, the guidance encourages innovators to engage in premarket consultation with the FDA for issues of specific concern.

Foremost of these is the potential allergenicity risk for foods from genome-edited plants. Consistent with its April 2023 letter to the industry on the food safety risks of transferring genes for proteins that are food, the FDA makes clear that developers that intend to transfer genes for proteins that are food allergens into new plant varieties must be acutely aware of safety risks, as well as allergen labeling requirements.

The FDA states that premarket consultation is recommended for foods from genome-edited plants that may have characteristics that warrant additional molecular, chemical or nutritional analyses.

The FDA includes a list of characteristics specifically developed to identify foods from genome-edited plants that may raise safety questions or regulatory considerations, including "whether an added substance, such as a newly expressed substance resulting from genome editing, is an unapproved food additive."

With respect to human foods, the list also includes plants that:

- Have been gene edited to contain modifications;
- Cause an increase in levels of potentially harmful components;

- An increase in the level and/or bioavailability of a nutrient;
- Change how the plant or food from the plant is used; or
- Introduce either new genes or genetic elements that do not naturally occur in that species, or additional copies of endogenous genes that are retained in the edited genome.

Premarket Meeting

The guidance significantly abbreviates the voluntary regulatory process for notifying the FDA about lower-risk foods from genome-edited plants. This second pathway, a premarket meeting, is introduced as an alternative to the conventional premarket consultation and marks a noteworthy change in FDA policy.

While the Center for Food Safety and Applied Nutrition has long made itself available for premarket meetings to discuss products in development, the agency has not previously formalized or created a public record of such meetings as an alternative to new plant variety consultations, or in the context of generally-recognized-as-safe notifications for food ingredients.

And, as the voluntary generally-recognized-as-safe notification process has been subject to criticism, this process too could be subject to challenge in the future.

A premarket meeting is designated as an alternative to premarket consultation appropriate for foods from genome-edited plants that do not have any of the characteristics identified in the guidance that may raise food safety questions.

As such, a premarket meeting is intended to familiarize the FDA with the types of foods from genome-edited plants entering the market and the steps taken to ensure their safety.

Critically, the premarket meeting does not require the level of information associated with a consultation and does not result in the same level of transparency.

The guidance states that simply a notice of the meeting will be posted on the FDA's website. It is not clear whether this new premarket meeting pathway is also available as an alternative for new plant varieties that are not genome-edited and are subject to the 1992 new plant variety policy.

Need for Further Clarification

Significant questions remain and should be the subject of further engagement with the FDA. These questions include the scope of the premarket meeting pathway, and whether it is also available for foods from genome-edited microorganisms, foods from genetically engineered plants, or other foods currently subject to a voluntary premarket consultation program, such

as the generally-recognized-as-safe notification pathway.

While the guidance was issued in final form, the FDA has stated that it will accept comments. It is also important to continue monitoring regulatory developments applicable this category of products more broadly, as the federal government works to respond to the 2022 executive order.

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[1] Emily Marden, "Risk and Regulation: U.S. Policy on Genetically Modified Food and Agriculture," Boston College Law Review, 2003.