Cornell University

CTL IP Series

IP Series #2: U.S. Regulatory Requirements for Gene Edited Plants

10/26/2023

CTL CENTER FOR TECHNOLOGY LICENSING AT CORNELL UNIVERSITY

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MORRISON FOERSTER

US Regulatory Requirements for Gene Edited Plants

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Agenda

- Coordinated Regulatory Framework
- EPA Regulation of Gene Edited Plants
- FDA Regulation of Gene Edited Plants
- USDA and the “SECURE” Rule

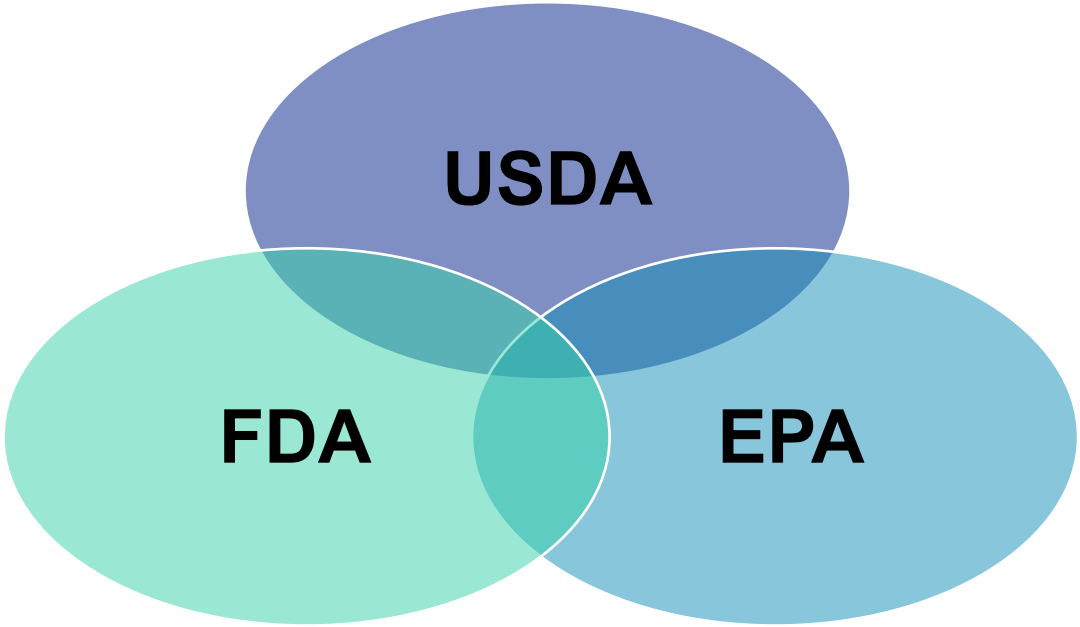
Nomenclature

FDA, USDA, and EPA use different terms to describe gene edited plants and food, which can make it difficult to compare:

- **EPA**: Plants created through biotechnology/genetic engineering (genetically modified)
- **FDA**: Bio-engineered food, gene edited (GE) food, and intentional genomic alterations (IGAs)
- **USDA**: Genetic engineering
  - Under USDA rules, GMO, which is a genetically modified organism or traditional transgenic plant, and gene-edited plants, are all considered "genetic engineering"

Coordinated Framework

In the U.S., Gene-Edited Plants and Food Are Regulated Under the Coordinated Framework



U.S. Agencies Have Different Responsibilities

U.S. Environmental Protection Agency (EPA)

- EPA regulates the use of pesticides and whether they are safe for humans and the environment.

U.S. Food and Drug Administration (FDA)

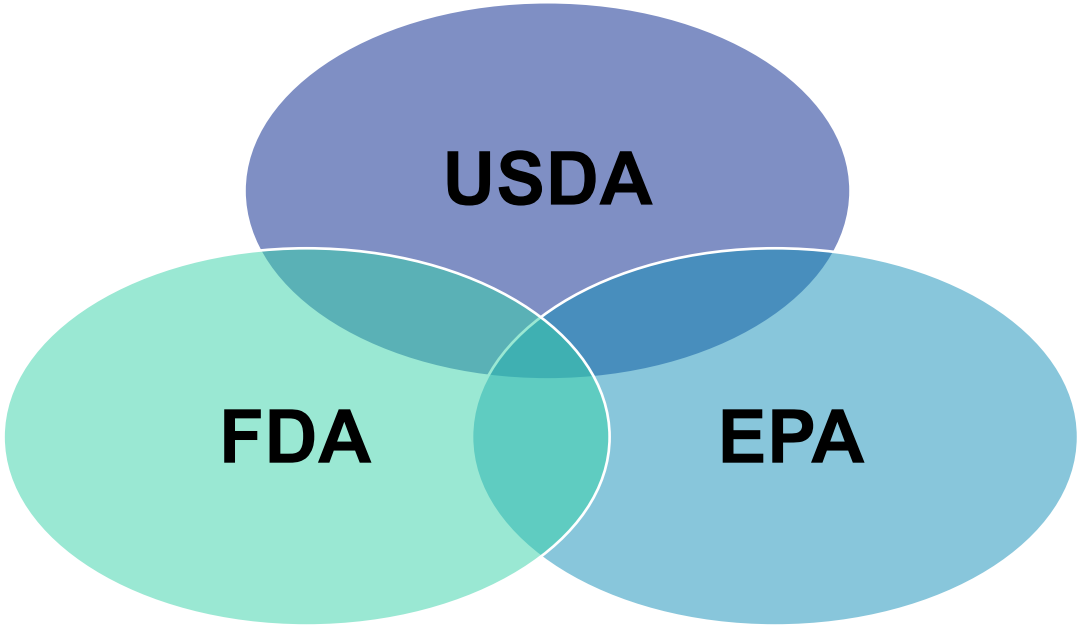
- FDA determines whether foods/feed grown from crops modified by modern biotechnology are as safe as their conventional counterparts

United States Department of Agriculture (USDA)

- USDA is responsible for protecting agriculture from pests and disease

- **A gene edited plant may be regulated by multiple agencies**
- **Protection goals of each agency determine how the product is evaluated and regulated**

Regulation of Gene Edited Plants Under the Coordinated Framework



How are Agencies Assessing Gene Edited Plants?

U.S. Environmental Protection Agency (EPA)

- New rules adopted and in force

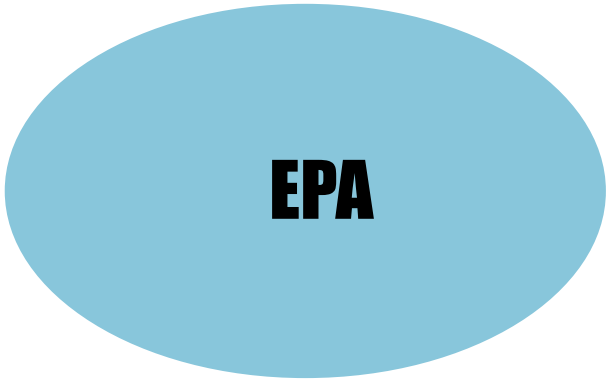
USDA-APHIS

- New rules adopted and in force

U.S. Food and Drug Administration (FDA)

- New rules in preparation
- Apply old rules

Coordinated Framework



EPA—Regulates Plant Incorporated Protectants

- EPA Regulates Plant Incorporated Protectants (PIP's) – **not** the plant
- A PIP is a pesticidal substance and the genetic material necessary to produce it in the plant
  - Under **FIFRA** (Federal Insecticide, Fungicide and Rodenticide Act) EPA evaluates PIPs for the effects on the environment and human health
  - Under **FFDCA** (Federal Food, Drug and Cosmetic Act) EPA evaluates PIPs that are proposed for use in food and feed

Plant Incorporated Protectants--PIPs

PIPs can be introduced into plants by classical plant breeding, gene editing, transgenic techniques, etc.

- **Examples of PIPs include:**
  - Plant protein toxic to insects eating a plant
  - dsRNA toxic to beetle larvae
  - dsRNA that degrades virus genetic material
  - Plant protein that prevents fungal growth
  - Loss of function PIPs through gene inactivation

Outline of the EPA PIP Regulatory Process

Consult with EPA Early and Often

1. Consult with EPA during R&D
2. Experimental Use Permit & Temporary Tolerance Exemption
3. Seed Increase Registration & Tolerance Exemption
4. Full Registration & Tolerance Exemption

- EPA may establish a tolerance exemption if PIP is determined to be safe.
- Safe means "reasonable certainty that no harm will result from exposure to the pesticide"

EPA PIP Regulation

EPA regulates all PIPs **except** those created through conventional breeding

- "Conventional Breeding" definition specifically *excludes* PIPs developed through biotechnology.
- Biotechnology includes genetic engineering, genetic engineering includes gene editing.

- **New EPA rules** create certain exemptions for certain genetically engineered PIPs.

New EPA Rules—May 2023

- EPA's New Rules allow for certain PIPs created through genetic engineering to be exempt where those PIPs:
  - Pose no greater risk than PIPs that EPA has already concluded meet safety requirements
  - Could have otherwise been created through conventional breeding

New EPA Rules—May 2023

1. Create an exemption for “PIPs created through genetic engineering from a sexually compatible plant”
2. Create an exemption for “loss-of-function PIPs”
3. Set forth an exemption eligibility determination process for PIPs
4. List exemption specific information required for submission
5. Issue recordkeeping requirements for PIPs.

PIPs created through genetic engineering from a sexually compatible plant

EPA: Genetic Engineering includes Gene Editing

Exempt PIPs Created through Editing from a Sexually Compatible Plant

Insert a "native gene"

- Insertion of a native gene to produce a substance identical in sequence to the pesticidal substance identified in the source plant.

Modify an existing gene to create a "native allele"

- Modifications of an existing native gene to match specific sequence(s) in a native allele of that gene.

Limitations of “Native gene” and “Native Allele”

- The pesticidal substance is limited to those from plants that are **sexually compatible** with the recipient plant
  - **Excludes** transgenes that could be moved between sexually compatible plants through conventional breeding
  - Transgenes = recombinant DNA

Examples of Exempt PIPs from Sexually Compatible Plants-I

EPA: Genetic Engineering includes Gene Editing

- **Insect resistant trait** is moved through genetic engineering from a resistant variety of corn to another variety of corn

- **Commercial potato variety** is genetically engineered to match a variation found in a disease resistant wild potato resulting in disease resistance.

Examples of Exempt PIPs from Sexually Compatible Plants-II

EPA: Genetic Engineering includes Gene Editing

- **Squash** is genetically engineered to replace the coding region of a gene with the coding region (i.e., only exons, no introns) of an allele found in a wild squash variety, resulting in increased insect resistance.
- **Banana** is genetically engineered to edit the regulatory region of an R gene to match a polymorphism identified in another variety of banana, resulting in increased expression of the R protein and disease resistance.

Example of Non-Exempt PIP

A bacterial endotoxin from *B. thuringiensis* that was engineered into plant "A" (source plant) would **not** qualify as a native gene to be used in plant "B" (recipient plant) as *B. thuringiensis* and plant "B" are not sexually compatible.

Loss of Function PIPS

Exemption for “Loss-of-function PIPs”- I

- “Loss-of-function PIPs” are characterized by a modification that leads to the reduction or elimination of the activity of a gene, which then results in a pesticidal trait
  - e.g. Inactivation of a gene coding for a plant receptor confers disease resistance.
- There must be a direct relationship between the loss of function of the native gene and the pesticidal effect

Exemption for “Loss-of-function PIPs”- II

- It is not a “loss-of-function PIP” if the loss of a native allele affects a second gene, which then produces a pesticidal substance.
- EPA regulates the modified genetic material that confers the pesticidal effect as the pesticidal substance and active ingredient.
- The loss-of-function PIP does not need to have been previously identified in a sexually compatible plant and there are no sequence specific requirements.

Exempt “Loss-of-function PIPs”

- **Disease resistant tomato:** A tomato has been genetically modified by disrupting a gene that encodes for a plant virus receptor.
  - The disruption causes a loss-of-function of the receptor, so that the virus is unable to infect the tomato and cause disease.

Exempt “Loss-of-function PIPs”

- **Disease resistant potato**: A potato has been genetically modified by deleting part of a gene encoding for a transcription factor.
  - Although the exact mode of action is not known, as transcription factors can result in the up or down regulation of other genes, the deletion in the gene for the transcription factor results in disease resistance in the potato.

Not Considered to be a Loss-of-Function PIP

- **Insect resistant blueberry bush**: A blueberry bush has been genetically modified by deleting part of a repressor gene that controls production of a pesticide substance.
- Loss-of-function of the repressor activity directly results in the increased expression of a known gene which encodes a pesticidal substance, conferring insect resistance.
- The PIP is the pesticidal substance

***Although the above example is not considered to be a loss-of-function PIP, it is still a PIP and may be exempt if it meets the criteria for PIPs created from sexually compatible plants.**

Multiple PIPs Within a Single Plant

- The exemptions do not limit the number of PIPs that can be created in a single recipient plant.
- Changes to multiple genes in a single recipient plant are allowed, so long as each resulting PIP individually meets the exemption criteria.
- EPA considers multiple native gene insertions of the same gene to be **one** PIP, so the criterion related to safe expression levels in food plants would apply to the overall expression level from all inserted gene copies.
- Similarly, a single loss-of-function PIP may require modification of several homologous genes of a native gene in a recipient plant.

Exemption Eligibility Determination Process

For a genetically engineered PIP to be eligible for exemption a developer must do at least **one** of the following:

- Request EPA confirmation.
- Self-determination (currently only available for loss-of-function PIPs).

Although "PIPs created through genetic engineering from a sexually compatible plant" are not currently eligible for the self-determination option, EPA intends to reconsider this in future rulemakings once the Agency and developers have gained experience.

- All submissions are required to be made electronically through EPA's CDX portal.

Information Required to be submitted to EPA-I

Biology of plant—

- Identity of the recipient plant, including genus and species
- Information to demonstrate that source and recipient plant are sexually compatible

Pesticidal trait—

- Description of measures taken to ensure no engineering components are present in final product
- Description of measures taken to maximize likelihood modification is limited to intended modification

Information Required to be Submitted to EPA-II

Molecular Characterization

- Nucleic acid sequence comparison of PIP between recipient plant and comparators
- Amino acid sequence for proteinaceous PIPs

History of safe use

- If substance is an allergen or mammalian toxin (e.g., solanine), describe how conventional breeding practices are being used to ensure that it does not exceed human dietary safety levels in the food plant
- If substance is from a wild relative, describe why the PIP is not anticipated to pose a hazard to humans or the environment

Extension of Exemption to Other Varieties of Same Species

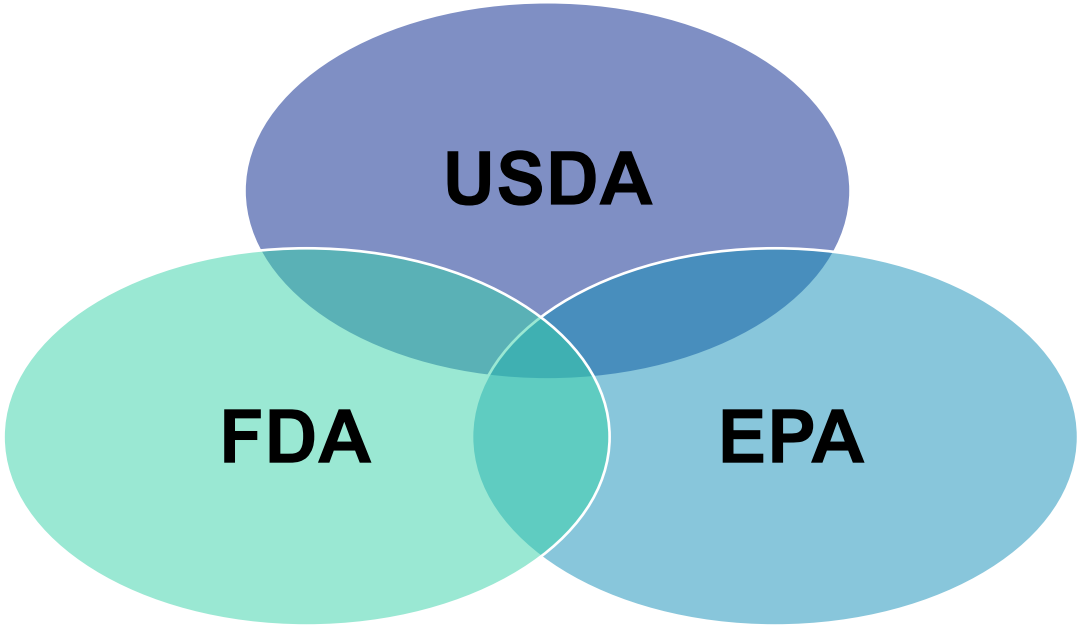
An exemption can be extended in two ways:

- The exempted PIP is moved through conventional breeding into other varieties.
- If the same submitter produces the identical substance through genetic engineering in another variety without any further modifications of the regulatory region (“PIPs created through genetic engineering from a sexually compatible plant”)
- Or the same submitter targets the same native gene in a different plant variety to create a “loss-of-function PIP” through genetic engineering (“Loss-of function PIPs”).

Multiple PIPs within A Single Plant

- Changes to multiple genes in a single recipient plant are allowed, so long as each resulting PIP individually meets the exemption criteria.
- The fee for an EPA determination applies to each individual PIP, meaning that if one plant contains multiple **unique** PIPs, the fee would apply multiple times.
- In the instance of modifying/inserting the same gene multiple times across the genome, the fee is only applied once, as the application contains only one PIP.

Regulation of Gene Edited Plants Under the Coordinated Framework

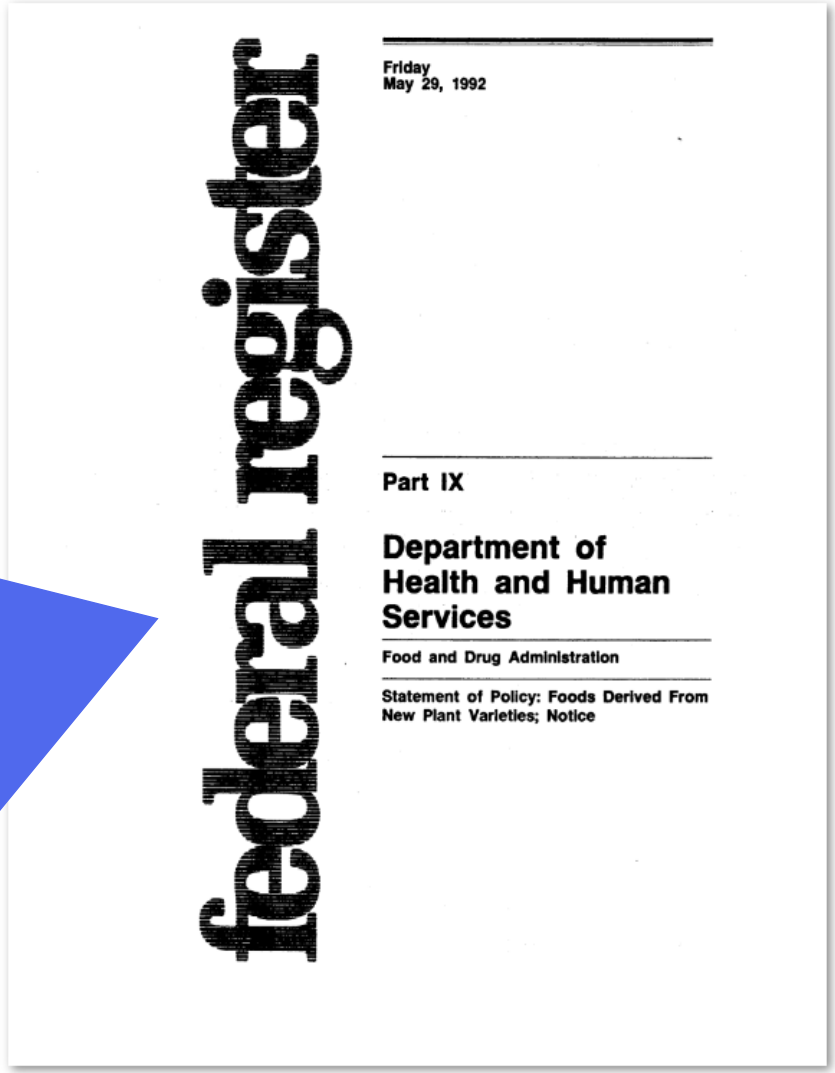


FDA Regulation of Gene Edited Plants

No Different Safety Standard for GM Foods

"Any genetic modification technique has the potential to alter the composition of food in a manner relevant to food safety, although, based on experience, **the likelihood of a safety hazard is typically very low**" and " … has **no basis for concluding that bioengineered foods differ from other foods in any meaningful or uniform way**, or that, as a class, foods developed by the new techniques present any different or greater safety concern than foods developed by traditional plant breeding".

57 FR 22983 (May 29, 1992) (emphasis added)


federal register

Friday
May 29, 1992

Part IX

Department of Health and Human Services

Food and Drug Administration

Statement of Policy: Foods Derived From New Plant Varieties; Notice

FDA-Transgenic Plants/Gene Edited Plants

- FDA is responsible for ensuring that the US food supply is safe, wholesome, sanitary and properly labeled
- FDA established pre-market consultation procedures to help ensure that the use of edited plants in food is safe and lawful
- Ex: a gene-edited pea and a burger made from that pea

FDA Consultation Procedures-I

Initial Consultation on Bioengineered Food

- FDA advises “early and often”
- Bioengineered food includes food made with edited plants
- Make FDA aware of new food and steps to ensure safety
- Obtain guidance specific to your new product

FDA Consultation Procedures-II

Consultation on Bioengineered Food

- FDA considers the safety of any new substances added to the food
  - Identity; structure/function
  - Potential toxicity/allergenicity
  - Dietary exposure/Nutritional impact
- FDA considers potential unintended effects
  - Genetic stability
  - Composition—nutrients and toxicants

FDA Consultation Procedures-III

Final Consultation

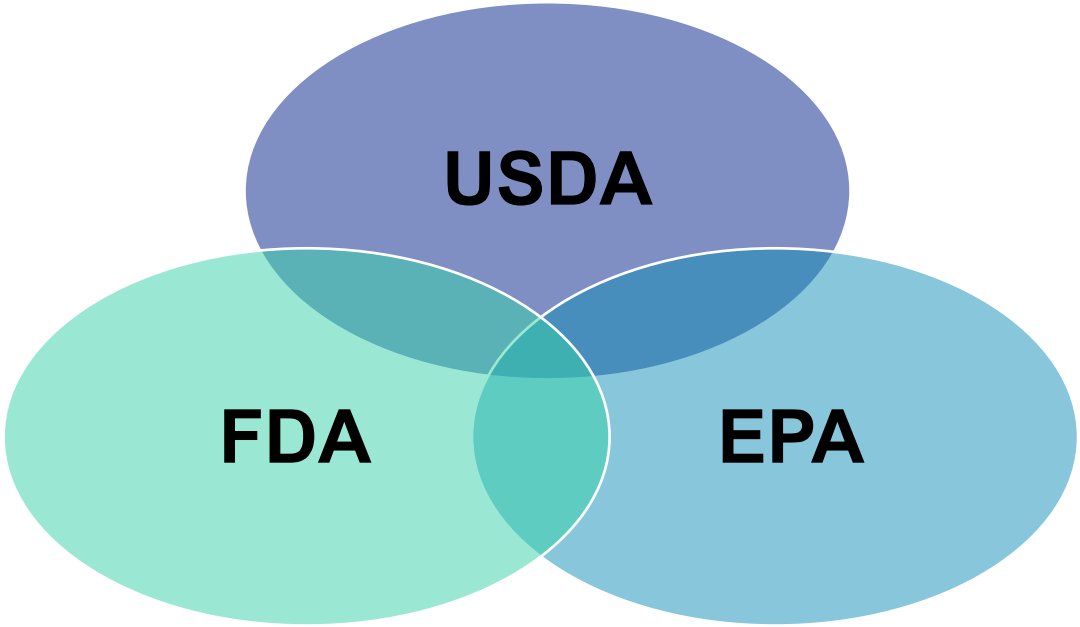
- FDA determines whether foods from the new plant variety are as safe as their conventional counterparts
- Once all safety and regulatory issues have been addressed, FDA sends the developer a letter stating **“at this time, FDA has no questions”**
- Completed consultations are listed on the FDA’s web site

FDA: Food from Gene Edited Plants

- In 2017, FDA issued a request for information regarding foods from plants produced using genome editing
- FDA received more that 500 comments
- FDA stated its intent to develop or update guidance *if appropriate* based on the comments
- A guidance would typically be published first in draft form and subject to public comment

Recent Executive Orders have underscored the urgency of regulatory clarity, but 6 years later there has still been no additional guidance

Regulation of Gene Edited Plants Under the Coordinated Framework



USDA and the "SECURE" Rule

USDA-APHIS

- Regulates the import, transportation, and environmental release of plants developed using **genetic engineering** that may pose a plant pest risk
- A “Plant Pest” is an organism that injures, causes damage or disease in a plant
- Genetic Engineering includes gene editing
- USDA regulates by requiring permits for movement of the plants
- Permit requires information on the intended trait and the genotype of the intended trait

New USDA/APHIS Rules for Gene Edited Plants

37 CFR Part 340

- Introduction of Organisms and Products Altered or Produced through Genetic Engineering which are plant pests
- Plant Pests have the potential for injury, damage to or disease in any plant or plant product resulting from introduction of the plant pest
- In US law since 1987
- May 18, 2020 APHIS announced their first comprehensive revision—the “SECURE” Rule

SECURE: “First Comprehensive Revision” Since 1987

Sustainable, Ecological, Consistent, Uniform, Responsible, Efficient

Is an APHIS Permit Required to Move/Release an Edited Plant?

- Was it made with "techniques that use **recombinant, synthesized, or amplified nucleic acids** to modify or create a genome?"

AND

- Does it have "a plant-trait-mechanism of **action combination that has not been evaluated by APHIS** in accordance with § 340.4 **or** that, as a result of such evaluation, **is subject to** the regulations"?

If **yes for both**, you need a permit, **unless** an exemption applies

Exemption Applicability is Self-determined

- If an exemption applies, you don't need to do anything
- You can move or release your edited plant
- …But if you are wrong, APHIS can sanction you
  - "APHIS may **seize, quarantine, treat, destroy, or apply other remedial measures** . . . to prevent dissemination of the organism."
  - APHIS has "**ample flexibility and broad civil penalty authority** to deter violations of the Plant Protection Act (PPA). For example, . . . statutory maximum penalties of **$1,000,000 per violation** for any person who willfully violates the PPA."

Exemption Applicability is Self-determined

- You may ***voluntarily*** reach out to APHIS for **confirmation** of your exemption determination
- When requesting a confirmation, include:
  - The scientific and common names of the plant
  - The intended and observed phenotype(s) of the trait(s)
  - A "clear understanding of the genetic change"
  - The specific exemption you think applies, and why
  - How you scientifically validated that the plant fits the exemption
- APHIS will respond within 120 days
- Confirmation requests & response letters **will be posted online** (CBI redacted)

SECURE Rule Exemptions: Gene Edited Plants

§ 340.1(b)(1)

§ 340.1(b)(2)

§ 340.1(b)(3)

§ 340.1(b)(4)

§ 340.1(c)

§ 340.1(d)

§ 340.5(c)

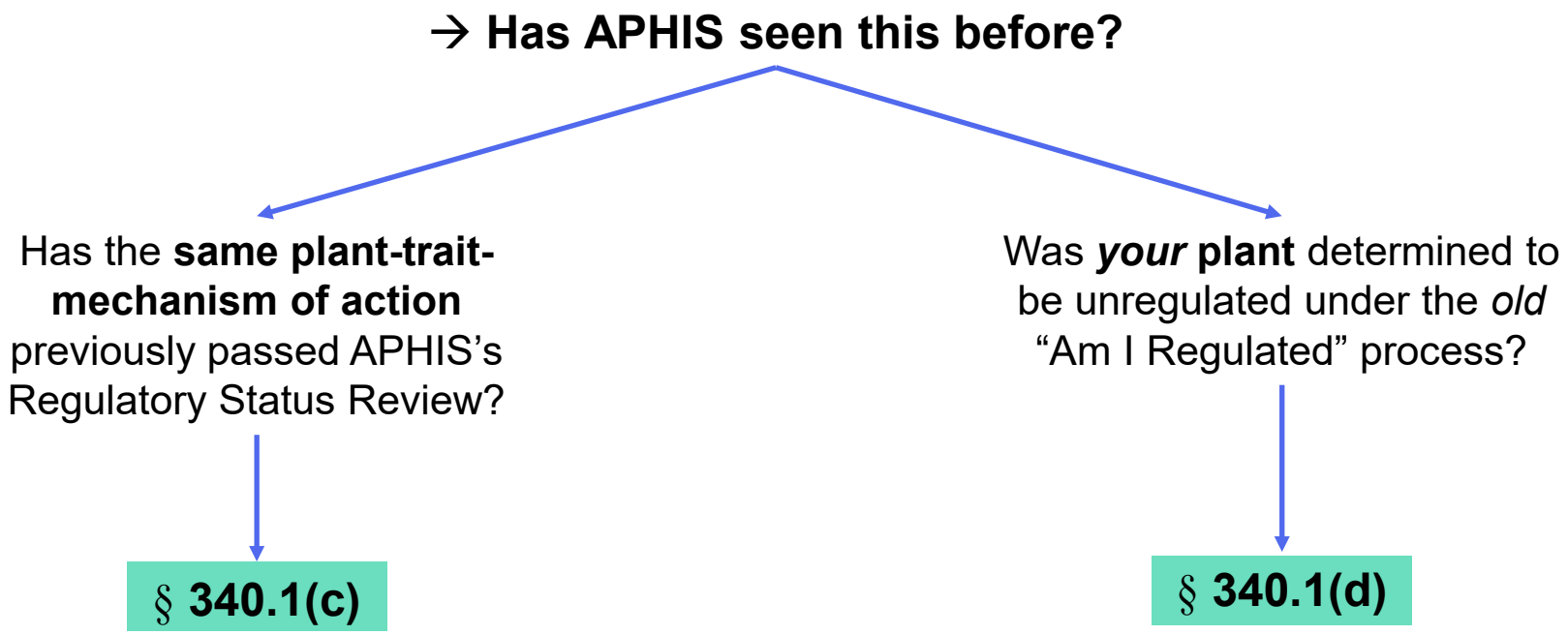
§ 340.5(g)

Secure Rule Exemptions §§ 340.5(c) and (g):

§ 340.5(c): "***Exemption for GE Arabidopsis thaliana*.** A permit for interstate movement is not required for GE *Arabidopsis thaliana*, provided that it is moved as a secure shipment, the modified genetic material is stably integrated into the plant genome, and the modified material does not include the complete infectious genome of a plant pest."

§ 340.5(g): "***Exemption of certain plant-incorporated protectants*.** A permit is not required for the movement of any GE plant modified solely to contain a plant-incorporated protectant (PIP) that is currently **registered** with EPA."

Secure Rule Exemptions §§ 340.1(c)-(d):



Secure Rule Exemptions §§ 340.1(b)(1-3)

- **A plant that contains a single modification of a type in one of the following three categories is exempt from regulation:**
  - A change resulting from cellular repair of a targeted DNA break in the absence of an externally provided repair template; or
  - A targeted single base pair substitution; or
  - Introduction of a gene known to occur in the plant's gene pool, or a change in a targeted sequence to correspond to a known allele of such a gene or to a known structural variation present in the gene pool.

More on § 340.1(b)(1)

§ 340.1(b)(1): "The genetic modification is a change resulting from cellular repair of a targeted DNA break in the absence of an externally provided repair template"

- Single targeted breaks only
- Basically, the same result as conventional breeding

More on § 340.1(b)(2)

§ 340.1(b)(2): "The genetic modification is a targeted single base pair substitution"

- Single modifications only
- Basically, the same result as conventional breeding

More on § 340.1(b)(3)

§ 340.1(b)(3): "The genetic modification introduces a gene known to occur in the plant's gene pool, or makes changes in a targeted sequence to correspond to a known allele of such a gene or to a known structural variation present in the gene pool"

- CAN COVER >1 MODIFICATION within a gene
- Does NOT apply if your modification results in a gene NOT known to occur in the gene pool
- "APHIS' intention in § 340.1(b)(3) is to exempt from regulation a product that could be *practically expected to be pursued and achieved* in a conventional breeding program"

§§ 340.1(b)(1)-(3): Flow Chart

→ Did you modify just *one gene* or *one pair* of homologous chromosomes? (excluding off-target changes)

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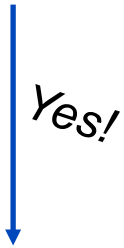


Does your modified sequence match a known allele in the plant's gene pool?

§§ 340.1(b)(1)-(3): Flow Chart

→ Did you modify just *one gene* or *one pair* of homologous chromosomes? (excluding off-target changes)

Yes!

Does your modified sequence match a known allele in the plant's gene pool?

Yes!

§ 340.1(b)(3)

§§ 340.1(b)(1)-(3): Flow Chart

→ Did you modify just *one gene* or *one pair* of homologous chromosomes? (excluding off-target changes)

Yes!

Does your modified sequence match a known allele in the plant's gene pool?

No…

Did you make just 1 targeted change?

Yes!

§ **340.1(b)(3)**

§§ 340.1(b)(1)-(3): Flow Chart

→ Did you modify just *one gene* or *one pair* of homologous chromosomes? (excluding off-target changes)

↓ *Yes!*

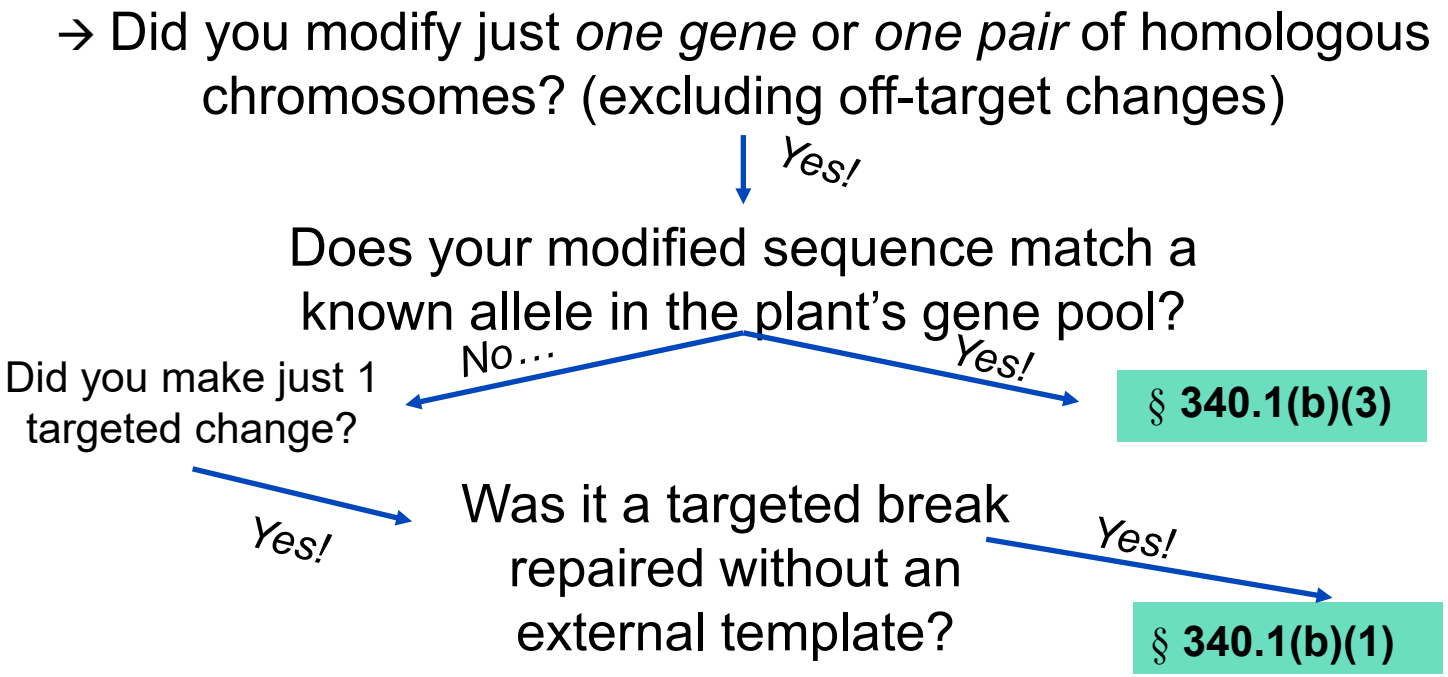
Does your modified sequence match a known allele in the plant's gene pool?

Yes! → § **340.1(b)(3)**

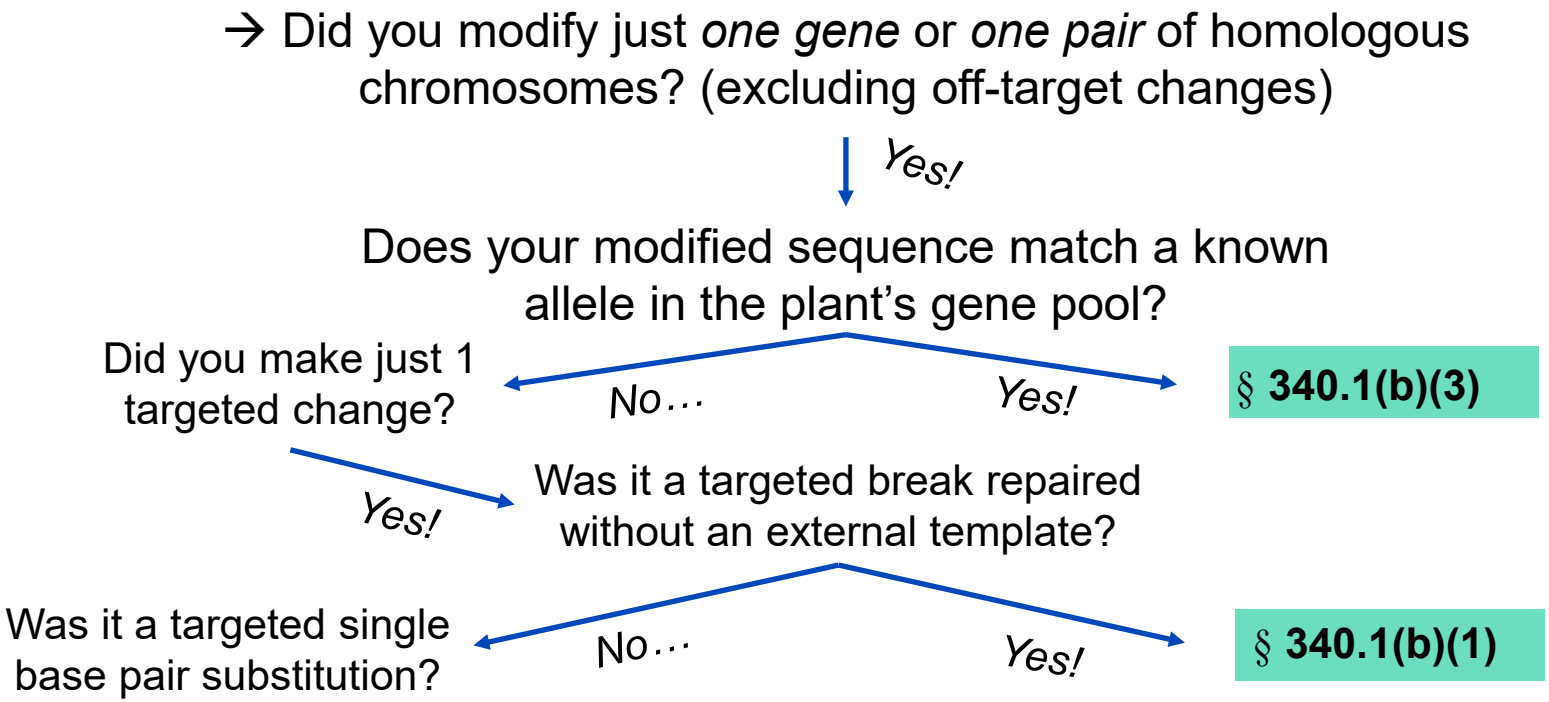
No… → Did you make just 1 targeted change?

Yes! → Was it a targeted break repaired without an external template?

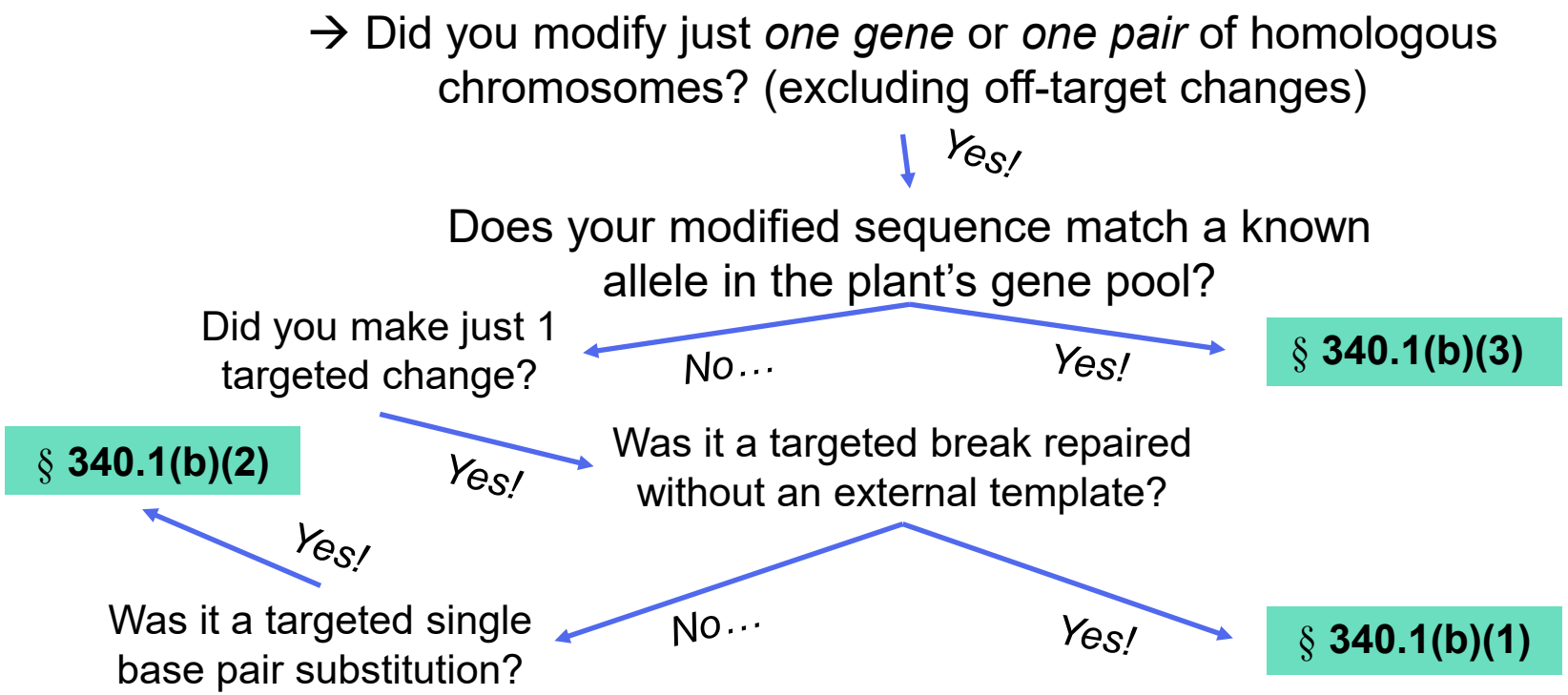
§§ 340.1(b)(1)-(3): Flow Chart



§§ 340.1(b)(1)-(3): Flow Chart



§§ 340.1(b)(1)-(3): Flow Chart



§ 340.1(b)(4):

§ 340.1(b)(4): "The Administrator may propose to exempt plants with additional modifications, based on what could be achieved through conventional breeding.

Such proposals may be Agency-initiated, and follow the process in paragraph (b)(4)(i) of this section, or in response to a request made in accordance with paragraph (b)(4)(ii) of this section…"

- Anyone can make a (b)(4)(ii) request

What About Combinations of Modifications?

"As a general matter, **APHIS does <u>not</u> believe that combinations of modifications** made simultaneously or sequentially in the same plant will **initially qualify** for an exemption under SECURE, with **two exceptions**."

1) **Single modifications that are exempt + conventional breeding → Offspring are exempt**
2) **Same set of plant-trait-MOA combinations that was previously deregulated**

"Plants with **other combinations** of modifications can be submitted to APHIS for review through the **RSR** process"

What if None of the Exemptions Apply?

…But you **really think** your specific case *should* be exempt?

→ § 340.4 Regulatory Status Review (RSR)

If you do <u>not</u> think it is exempt,

→ Apply for a permit (§ 340.5)

§ 340.4 Regulatory Status Review (RSR)

- Become someone else's §340.1(c) exemption!
- APHIS evaluates the GE plant's plant pest risk and determines whether it should be regulated or not
- Anyone can submit an RSR request
- APHIS will conduct an "initial review" within 180 days

Regulatory Status Review (RSR) Process

Did APHIS's initial review reveal a "plausible pathway by which the GE plant or its sexually compatible relatives would pose an increased plant pest risk"?

Regulatory Status Review (RSR) Process

Did APHIS's initial review reveal a "plausible pathway by which the GE plant or its sexually compatible relatives would pose an increased plant pest risk"?

No!

The GE plant is NOT subject to the SECURE rule

APHIS will post the plant, trait, and general description of the mechanism of action online

Welcome to the § 340.1(c) club

Regulatory Status Review (RSR) Process

Did APHIS's initial review reveal a "plausible pathway by which the GE plant or its sexually compatible relatives would pose an increased plant pest risk"?

No!

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Welcome to the §340.1(c) club

Yes…

Do you want to push harder?

Regulatory Status Review (RSR) Process

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Welcome to the §340.1(c) club

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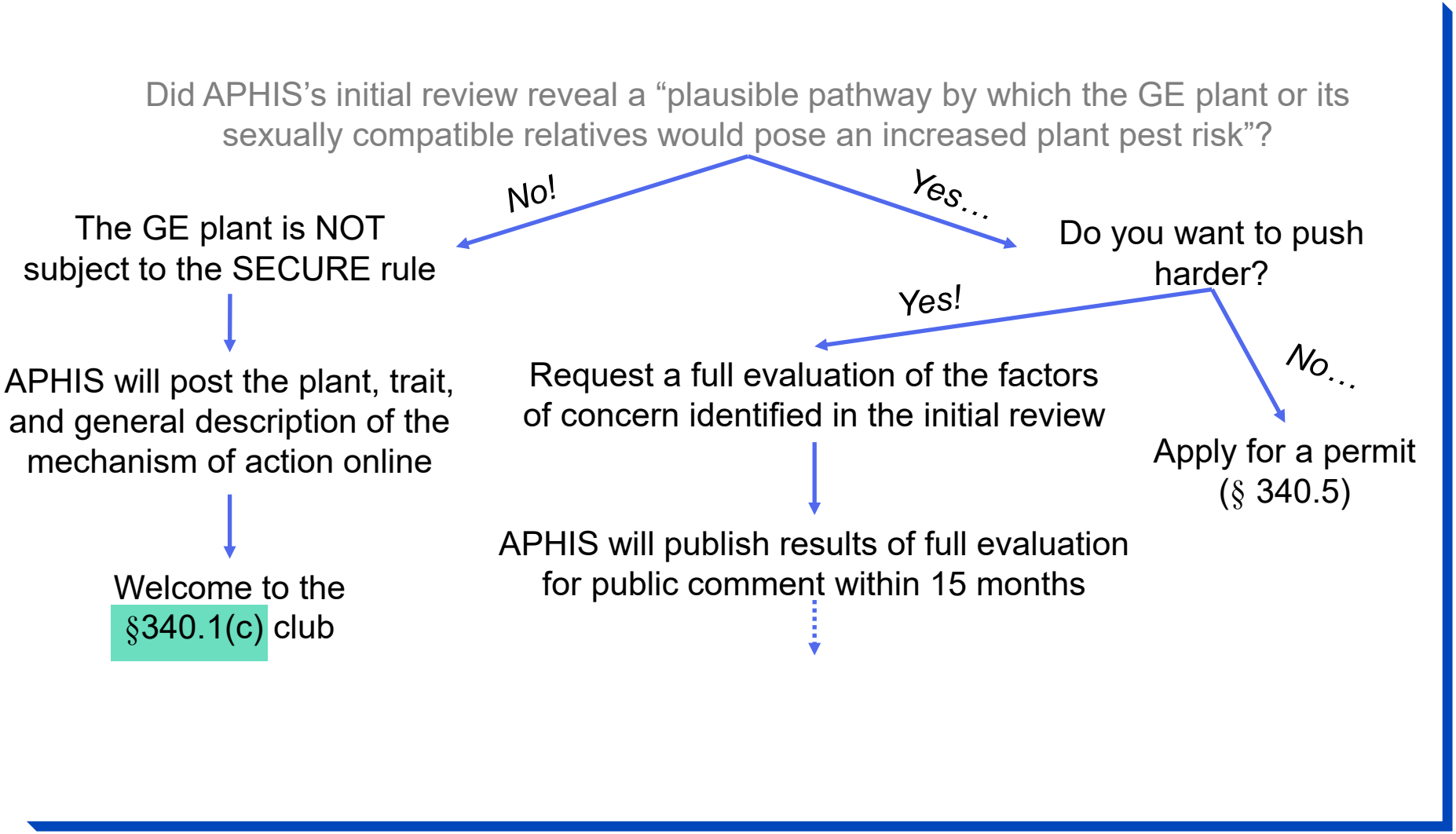
No…

Apply for a permit (§ 340.5)

Regulatory Status Review (RSR) Process



Regulatory Status Review

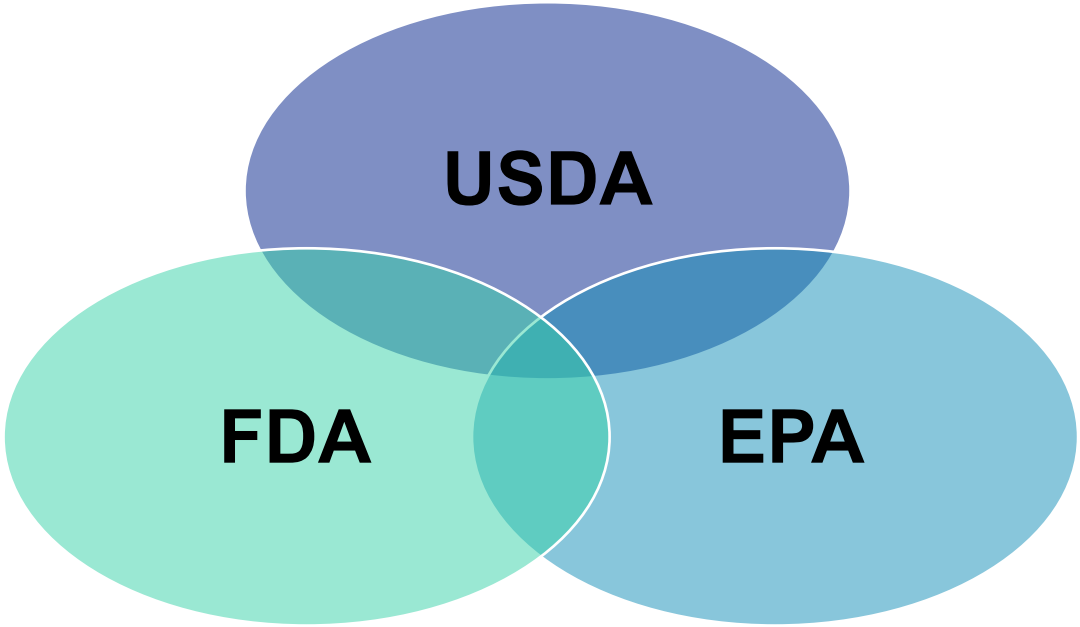
Regulatory Status Review information is all available on-line:

- USDA APHIS | Regulatory Status Review Table
- USDA APHIS | Confirmation Letters

Apply for a Permit:§ 340.5

- Permit requires information on the intended trait and the genotype of the intended trait
- APHIS will approve or deny the permit within:
  - 45 days of receipt of a complete application for a permit for interstate movement or importation into the U.S.
  - 120 days of receipt of a complete application for a permit for release into the environment
  - 120-day period may be extended for an environmental impact statement.

Regulation of Gene Edited Plants Under the Coordinated Framework



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Any Questions?

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