# New Developments in Federal Regulation of Biotechnology

## Pharmaceutical EHS Counsel Roundtable

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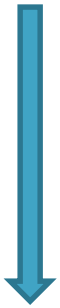
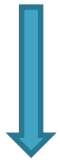
BEVERIDGE & DIAMOND PC

# Timeline of New Developments

- Feb. 5, 2016 – APHIS notice of potential changes



- Sept. 18, 2016 – Coordinated Framework Update (draft)



- Jan. 4, 2017 – Coordinated Framework Update (final)

- Jan. 18, 2017 – FDA guidance on GE animals (draft)
- Jan. 18, 2017 – FDA guidance on GE mosquitoes (draft)
- Jan. 19, 2017 – FDA docket on GE plants
- Jan. 19, 2017 – APHIS proposal on GE organisms
- Jan. 19, 2017 – APHIS proposal on plant pests

# Overview

Coordinated Framework for the Regulation of Biotechnology

FDA Developments

APHIS Developments

# What is the Coordinated Framework for the Regulation of Biotechnology?

- First issued by White House OSTP in 1986
- Answers the question:

"How Should the Federal Government Regulate Biotechnology?"

Existing Federal Statutes and Authorities

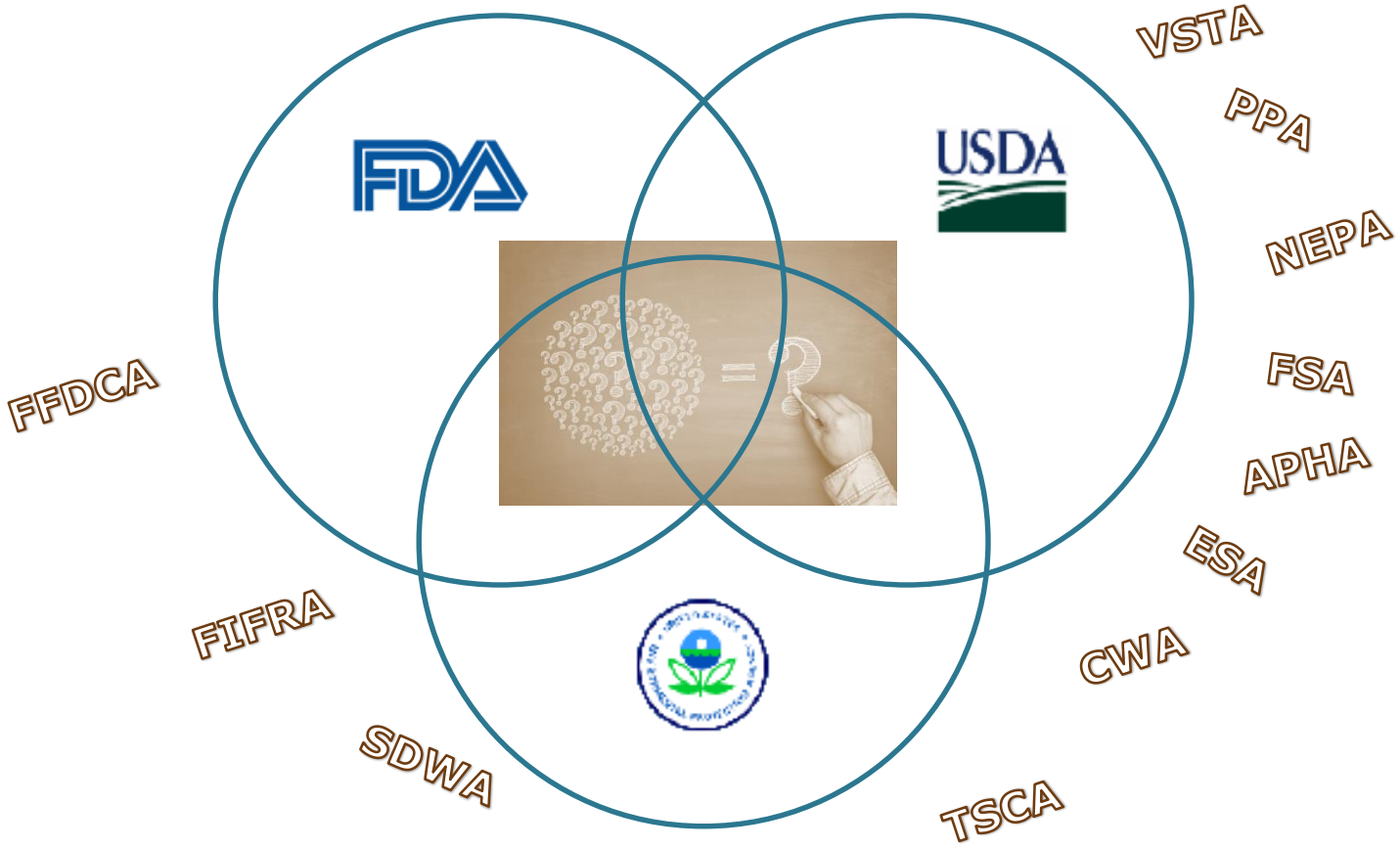
# What is the Coordinated Framework for the Regulation of Biotechnology?

- Sought to:

> "achieve a **balance** between regulation adequate to ensure the **protection of health and the environment** while maintaining sufficient regulatory **flexibility** to avoid impeding innovation."

> Use existing statutes to assure **reasonable safeguards for the public and the environment** through the generation of a "smooth, **understandable** regulatory oversight process"

# A "smooth, understandable regulatory oversight process"



# What is the Coordinated Framework for the Regulation of Biotechnology?


Protect agricultural plants and agriculturally important natural resources from damage caused by organisms that pose plant pest or noxious weed risks.

Protect livestock from disease-causing pests.

Ensure safety and efficacy of veterinary biologics.

Prevent and eliminate unreasonable adverse effects on the environment

Ensure human and animal food is safe, sanitary, and properly labeled.


Ensure human and animal drugs are safe and effective.

Ensure the reasonable assurance of the safety and effectiveness of devices intended for human use.

Ensure cosmetics are safe and properly labeled

# Key Statutory Authorities

FDA

FFDCA

USDA

PPA
NEPA
ESA
FSA
APHA
VSTA

FIFRA
FFDCA
ESA
SDWA
CWA
TSCA

# Pharmaceuticals & Biotechnology

- Drugs Produced by GE Plants
- Drugs Produced by GE Animals

# Modernizing the Coordinated Framework

## 1992 update:

- set forth a risk-based, scientific basis for the oversight of activities that introduce biotechnology products into the environment
- Affirmed that Federal oversight **should focus on a product's characteristics, rather than the process by which the product is created**
- Extent and type of oversight should be commensurate with gravity and type of risk being addressed, the costs of alternative oversight options, and the effect of additional oversight on existing safety incentives

# Modernizing the Coordinated Framework

## July 2015 memo acknowledged:

- **Unnecessary** costs and burdens associated with uncertainty about agency jurisdiction
- **Lack** of predictability of timeframes for review
- **Limited** ability of small and mid-sized companies to navigate the regulatory process
- **Limited** ability of the public to understand easily how product safety is assured
- **Reduced** potential for economic growth, innovation, and competitiveness
- Advances in science and technology that have "**dramatically altered**" the biotechnology landscape since 1992
- Status of genome-editing

# Modernizing the Coordinated Framework

- Tasks were assigned to a newly established Biotechnology Working Group (EPA, FDA, USDA)

Which product areas are within authority and responsibility of each agency?

What roles will each agency play for different product areas?

What standard mechanism for communication/coordination will be established among agencies?

What mechanisms/timelines will be established to minimize delays, support innovation, and protect health/environment?

# Modernizing the Coordinated Framework: Timeline

- Biotechnology Working Group formed (July 2015)
- Request for Information (October 2015)
- Three public meetings (October 2015 – March 2016)
- NAS announces study called "Future Biotechnology Products and Opportunities to Enhance Capabilities of the Biotechnology Regulatory System" (January 2016)
  - Report currently anticipated "early 2017"
- Proposed Update Issued, with National Strategy for Modernizing Regulation of Biotechnology (September 18, 2016)
- Final Update and Strategy Issued (January 4, 2017)

# Coordinated Framework Update

Assures public that current regulatory system "effectively protects health and the environment"

Observes potential for "unnecessary costs and burdens"

- Ongoing uncertainty over agency jurisdiction
- Lack of predictable timeframes for review

Recognizes need to clarify authority and responsibility over new technologies

# Coordinated Framework Update


Regulates biotechnology products that may (i) introduce pests or cause disease to livestock under APHA, (ii) be deemed plant pests or noxious weeds under PPA, or (iii) be used in veterinary biologics under VSTA; also reviews safety of meat, poultry, eggs, or fish from GE animals intended for human consumption

Regulates chemical pesticides, microorganisms, biochemicals, and PIPs under FIFRA and FFDCA; also responsible for microbial biotechnology applications under TSCA


Regulates human and animal food derived from GE plants and animals; also human drugs, biologicals, and medical devices derived from GE sources under the FFDCA

# Coordinated Framework Update: Strategy

- Increase **transparency**
  - Work with stakeholders to identify impediments to innovation
  - Streamline processes
  - Reduce costs and response times

- Increase **predictability** and **efficiency**
  - Develop plan for periodic assessments of new products
  - Ensure product evaluations are risk-based and grounded in best available science
  - Identify regulatory and policy changes to improve expeditious risk assessments

- Support **science** that underpins the regulatory system
  - Develop a coordinated plan to support science that informs biotechnology product assessments

# Coordinated Framework Update: Case Studies

**Case Study #7: A Hypothetical Genetically Engineered (GE) Rabbit**

*A hypothetical animal is genetically engineered to make a therapeutic protein (recombinant insulin) for treatment of humans lacking this protein activity.*

**I. The product**

The rabbit (*Oryctolagus cuniculus*) genome is genetically engineered to express recombinant human insulin (rh insulin) for use as a therapeutic protein in the treatment of human patients lacking adequate functional insulin. The human insulin coding sequence is controlled by 5' bovine αS(1) casein promoter sequences to direct expression of recombinant insulin protein in rabbit milk. The construct is microinjected into fertilized oocytes and the resulting embryos are transferred to the oviduct of a recipient dam. Also encoded in the vector, and stably incorporated into the rabbit genome, are upstream and downstream regulatory sequences that enable expression of the included codon-optimized human insulin coding sequence in the rabbit and insulator sequences to minimize position effects at the locus of integration into the rabbit genome. Once a germline GE animal is identified as a lineage progenitor, it is bred to establish a lineage of GE rabbits used in insulin expression in milk.

**II. Which agencies have oversight and why?**

FDA The rDNA construct encoding the recombinant human insulin protein integrated in the genome of the GE rabbit is regulated as a new animal drug by the FDA Center for Veterinary Medicine (CVM); the rh insulin purified from the GE rabbit milk is regulated as a human drug by the FDA Center for Drug Evaluation and Research (CDER). Each product requires a separate approval.

**III. Developer responsibilities during hypothetical GE rabbit and insulin development (*e.g.*, the laboratory, farm, and clinic)**

The developer should initiate discussions with FDA/CVM once the lineage progenitor has been identified and the lineage is being characterized actively. FDA/CVM would open an investigational new animal drug file (INAD) into which the developer could submit data and information pertaining to the investigations leading to an application for approval pertaining to this GE rabbit lineage. For shipments of investigational GE animals, the developer must submit Notices of Claimed Investigational Exemption for a New Animal Drug (INAD Notice) to FDA/CVM.

Sponsors must meet all of the requirements for safety and effectiveness of the new animal drug (the construct encoding the rh insulin) prior to the approval of the rh insulin. After the product is approved, FDA codifies the approval of the new animal drug, publishes a Federal Register notice when the approval is codified, and posts on FDA's website a summary of the information on which this approval was based.

For the rh insulin, the sponsor must submit an Investigational New Drug (IND) application to FDA/CDER prior to clinical trial activities for the rh insulin product derived from these GE rabbits. The IND submission generally contains information, including preclinical data from animal pharmacology and toxicology studies; composition, stability, and manufacturing controls; and protocols for proposed clinical studies. The developer may seek pre-IND advice for issues related to the design of pharmacology, toxicology, and drug activity studies; data requirements for an IND application; initial drug development plans, and regulatory requirements for demonstrating safety and efficacy of the rh insulin product. If FDA approves the rh insulin product, FDA posts a notice of the approval and provides a summary of the safety information relevant to the approval on its website.

Note, under NEPA, the developer must submit to FDA EAs or claims of categorical exclusion as part of its INAD, NADA, IND, and NDA submissions.

**VII. Public engagement prior to commercialization**

FDA: If FDA approves the rh insulin product, FDA codifies the approval of the new animal drug, publishes a Federal Register notice when the approval is codified, and posts on FDA's website a summary of the information on which this approval was based.

# Coordinated Framework Update: Strategy

**The regulation of human drugs, biological products, and medical devices that are derived through the use of biotechnology is not the focus of this current effort**

# Regulation of Pharmaceuticals under the Coordinated Framework

| | ***Source Organism or Culture*** | | |
|---|---|---|---|
| **Product Area** | ***Genetically Engineered Plant*** | ***Genetically Engineered Animal*** | ***Genetically Engineered Microbe or Cultured Cell*** |
| Drug for Humans | FDA/CDER<br>USDA/APHIS (if plant poses a plant pest risk) | FDA/CVM<br>FDA/CDER | FDA/CDER |
| Drug for Animals | FDA/CVM<br>USDA/APHIS (if plant poses a plant pest risk) | FDA/CVM | FDA/CVM |


FDA

# FDA Regulation of Pharmaceuticals under the Coordinated Framework

- FDA regulates human drugs, biological products, and medical devices that are derived using biotechnology under the **same legal and regulatory provisions** as are applicable to the corresponding non-biotechnology products.
  - FDA regulates drug products produced by GE plants.
  - FDA regulates drug products produced by GE animals.
  - FDA also regulates GE animals under the "New Animal Drug" provisions of the FFDCA.

# FDA's NAD Authority

- FFDCA Sec. 201(g):

"drug" includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals"; and "**articles (other than food) intended to affect the structure or any function of the body of man or other animals**."

Examples:

- GE goats and chickens that produce human drugs
- AquaAdvantage Salmon (2015) (GE growth hormone)
- Oxitec Mosquito (GE sterilization)

# New Draft FDA Guidance

January 18, 2017:

- ***Guidance for Industry #187: Regulation of Intentionally Altered Genomic DNA in Animals***
  - Comments due April 19, 2017

- ***Guidance for Industry #236: Regulation of Mosquito-Related Products***
  - Comment period ended February 21, 2017

# New Draft FDA Guidance: GE Animals

- Expands range of technologies subject to NAD requirements under the FFDCA
  - Previously addressed rDNA modifications
  - Now covers "any heritable genomic alteration"
    - Includes random or targeted DNA sequence changes
    - Any other technologies that introduce specific changes to the genome of an animal
  - Each specific alteration to the animal genome constitutes a distinct NAD

# New Draft FDA Guidance: GE Mosquitoes

- Fundamentally different regulatory approaches taken to sterilized mosquitoes
  - FDA NAD jurisdiction
  - EPA FIFRA jurisdiction

- New guidance proposes that EPA will exclusively regulate "articles intended to function as pesticides by preventing, destroying, repelling, or mitigating mosquitoes for population control purposes"

- FDA will assert jurisdiction only over products that reduce virus or pathogen loads in mosquitoes or directly prevent mosquito-borne diseases

# New Draft FDA Guidance: Genome-Edited Plants

January 19, 2017:

- FDA opens docket for comments on the use of genome-editing techniques to produce **new plant varieties that are used for human or animal food**
- FDA intends to clarify its policy for the regulation of products derived from genome-editing techniques (including new technologies that use targeted nucleases or targeted oligonucleotides to modify a plant's DNA sequence by insertion, deletion, or substitution of nucleotides at a specific site in a plant's genome)
- Comments due April 19, 2017


USDA
APHIS

# APHIS's Plant Pest Authority

- Plant Protection Act Sec. 7711(a):
  - Regulates the importation, entry, exportation or movement of plant pests
  - "plant pests": protozoan, nonhuman animal, parasitic plant, bacterium, fungus, virus, infectious agent, pathogen
  - 7 CFR 330: regulates movement of plant pests
  - 7 CFR 340: regulates movement of GE plant pests

# APHIS's Plant Pest Authority

- Currently:
  - a GE organism is deemed a "regulated article" if it has been genetically engineered using a donor organism, recipient organism, vector or vector agent that is a plant pest
  - *E.g., Agrobacterium*

# Proposed Programmatic APHIS Changes -- Background

- 2008: APHIS proposes to expand the scope of its regulatory program beyond plant pests, consistent with its additional PPA authority over noxious weeds.
  - Explains that technological advances over the last two decades "led to the possibility of developing GE organisms that do not fit within the plant pest definition, but may cause environmental or other types of physical harm or damage covered by the definition of noxious weed in the PPA."
  - Does **not** suggest any changes to the definition of the term "genetic engineering" itself.

# Proposed Programmatic APHIS Changes -- Background

- 2015: Thousands of comments later, APHIS withdraws its proposed rule, and instead initiates a series of public webinars and outreach to more broadly evaluate alternative approaches to the regulation of biotechnology under the PPA.

- 2016: APHIS again raises the possibility of revising its biotechnology regulatory program, citing interest in more "efficiency and precision" in its regulations.

  - Considers replacing its defined term "regulated article" with a narrower "regulated organism" term encompassing an "organism developed using biotechnology" that APHIS has definitively found to pose a plant pest or noxious weed risk warranting APHIS regulation.

# APHIS Proposal to Revise Regulation of GE Organisms

January 19, 2017

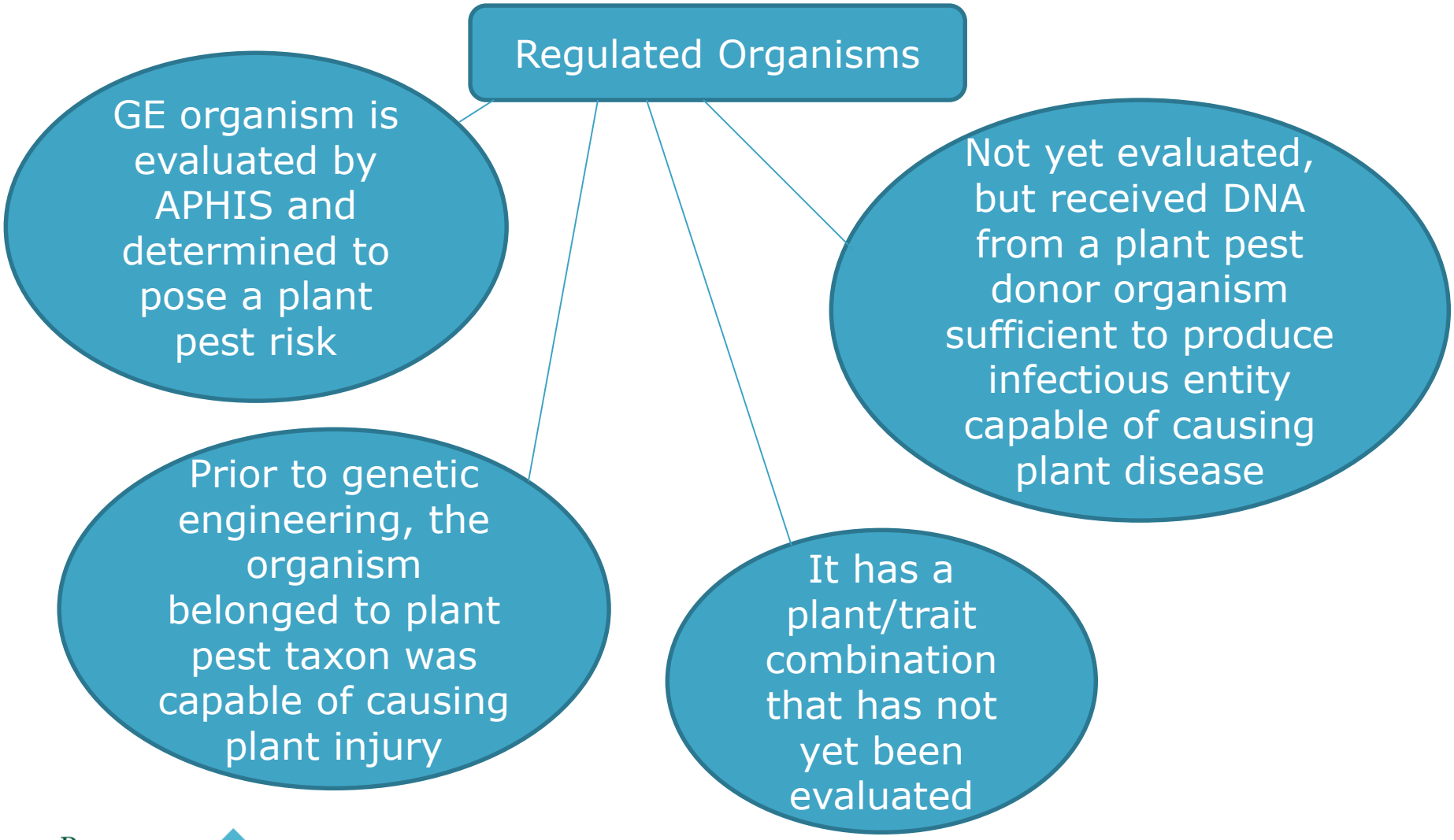
- Proposal represents first comprehensive revision of APHIS biotechnology regulations since 1987
- Comments due by June 19, 2017

# APHIS Proposal to Revise Regulation of GE Organisms

APHIS will no longer consider GE organisms to be "regulated organisms" solely because of plant pest status of donor, vector, or vector agent used in the process

If a GE organism is not a regulated organism, it may be imported, moved interstate, or released into the environment without further restriction

# APHIS Proposal to Revise Regulation of GE Organisms



# APHIS Proposal: PMPIs

- Plant-Made Pharmaceuticals
  - "**most, if not all**" GE plants that produce plant-made pharmaceuticals and industrials (PMPIs) currently under APHIS permits could be determined not regulated because they do not represent risk as a plant pest or noxious weed
  - Plants can be grown outdoors without APHIS permits or oversight

# APHIS Proposal: PMPIs

- What happens if unevaluated PMPI products are introduced into human or animal food supply?
  - Authorize new Federal agency oversight under a new statute or amended existing statute
  - EPA or other agencies can expand oversight based on existing authority

# APHIS Proposal to Revise Regulation of Plant Pests

January 19, 2017

- Revives 15-year effort to clarify authority over plant pests
- Comments due by April 19, 2017

# APHIS Proposal to Revise Regulation of Plant Pests

APHIS will establish a list of plant pests that may be imported or moved without a permit or other restrictions

(1) Is the organism ubiquitous within its entire U.S. range?

(2) Is the organism sufficiently attenuated?

(3) Is the organism regulated by another Federal agency?

Bacteria, fungi, insects, cockroaches, mites, nematodes, viruses

# APHIS Proposal to Revise Regulation of Plant Pests

- Petition process to request addition of a plant pest to exemption list
- General "web-based" permits to authorize interstate movement of certain "low-risk" plant pests

# Questions?

# Backup Slides

# Modernizing the Coordinated Framework

## Emphasized need for improvements that:

- Maintain high standards based on **best available science** and that deliver appropriate health and environmental protection
- Establish transparent, coordinated, predictable, and efficient regulatory practices across agencies with overlapping jurisdiction
- Promote public confidence in the oversight of the products of biotechnology through clear and transparent engagement

# Modernizing the Coordinated Framework

## Objectives:

- Develop an updated Framework to clarify roles/responsibilities of relevant agencies
- Formulate a long-term strategy equipped to efficiently assess the risks associated with future biotechnology products while supporting innovation and protecting health
- Commission an external, independent analysis of the future landscape of biotechnology products (NAS has now been asked to do this)

# Modernizing the Coordinated Framework

- Formulate a long-term strategy equipped to efficiently assess the risks associated with future biotechnology products while supporting innovation and protecting health, including:
  - Ensure that product evaluations are risk-based and grounded in best available science
  - Identify changes to authorities, regulations, and policies that could improve agencies' abilities to assess "expeditiously" the potential risks and impacts of GE products while ensuring transparency, predictability, and efficiency of regulatory oversight
  - Initiate modernized, user-friendly set of tools for regulatory decision-making, including digital services to improve interactions among agencies, the public, and product developers

# Proposed Programmatic APHIS Changes -- Background

- Consistent with PPA authority to regulate "plant pests", APHIS regulates the introduction of certain GE organisms that may cause injury or harm to plants.
  - When issued in 1987, APHIS's implementing regulations at 7 C.F.R. Part 340 addressed nearly all GE plants, since most of the then-existing plant-based GE technologies involved the use of modified plant pests such as *Agrobacterium* to transfer new genes to plants.
- "Genetic engineering" is defined under Part 340 to mean "the genetic modification of organisms by recombinant DNA techniques."