Regulation of Biotechnology Products—Clarifying Roles and Responsibilities through Hypothetical Case Studies

Target Audience

This document is intended to provide general information to developers who believe they have, or are uncertain as to whether they may have, a biotechnology product that is subject to regulation under one or more of the Federal laws described in the *Coordinated Framework for Regulation of Biotechnology (CF)*. This document uses case studies as a means of demonstrating how a developer might navigate the regulatory framework, starting from research activities in the laboratory, to full commercialization of the product. Certain products may also have post market monitoring and reporting requirements that are not described in this document. More information on such requirements is available in relevant agency regulations and guidances. The individual regulatory path that a product takes is based on its characteristics and intended use, as one or both can affect the regulatory status and relevant requirements established in the various regulations and policies that underlie the *Coordinated Framework*. Graphic illustrations associated with each case study highlight typical major milestones during the product development and how each step relates to the regulatory agencies and their legal authorities.

The contents of this document are draft and still under review at the various agencies. When the contents are finalized, the document will be incorporated into an update to the Coordinated Framework, which will undergo a formal public comment period.

Introduction

The primary Federal agencies that regulate biotechnology products are the US Food and Drug Administration (FDA), the US Environmental Protection Agency (EPA), and the US Department of Agriculture (USDA). The CF, which describes how these agencies work together, using their statutory authorities to help ensure the safety of biotechnology products for humans, animals, and the environment, was published in 1986. The CF is based on laws older than the CF itself. These laws were enacted by Congress to address risks potentially associated with various types of products, e.g., food, drugs, pesticides.

The Case Studies

Experience gained over the nearly 30 years since publication of the CF can suggest the paths most frequently used by developers in navigating the regulatory framework, from research and development (R&D) through to commercialization. Representative experiences are outlined in this appendix in the form of case studies of hypothetical products. These case studies are not intended to represent actual products.

The case studies presented in this document were selected because they cover multiple biotechnology product areas with different characteristics and intended uses and because they illustrate how agencies coordinate their oversight under the CF. There are also other nuances, such as exemptions for certain products within the regulatory system that can affect the path forward. These will be touched on in the case studies as appropriate. The case studies presented here cover typical relevant milestones, from the identification of a potentially commercially viable biotechnology product, to research and development activities in the laboratory and the field, to commercialization. Figure 1 is a visual representation of the path each hypothetical product, associated with a case study, will typically take through the regulatory system.

Recognizing that intricacies exist in any regulatory system, the FDA, EPA, and USDA welcome and encourage developers of potential biotechnology products to contact the agencies at the early stages of product development so any questions related to regulatory status, safety, and/or effectiveness can be identified and adequately addressed. Contacting agencies at the early stages of product development may make the regulatory process more predictable for applicants. For contact information and additional resources please refer to the end of this document.

These materials, facts, and scenarios are purely hypothetical and presented for discussion purposes only. The content of these materials and this discussion do not necessarily reflect the view or policies of the Federal agencies and should not be

construed as an official Federal opinion or decision on any particular matter.

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Case Study #1: Hypothetical, Genetically Engineered (GE) Corn with Pesticidal Properties

A field crop, used for food for humans and animals, is engineered with a plant pest component to have pesticidal activity against certain insects.

I. The product

Corn (*Zea mays*) is genetically engineered to express a protein with pesticidal activity. The gene encoding the protein is isolated from the bacterium *Bacillus thuringiensis* and controlled by the cauliflower mosaic virus-derived 35S promoter (CaMV). The construct is integrated into a binary vector and introduced into the corn genome using *Agrobacterium*-mediated transformation. Also encoded on the vector, and stably incorporated into the corn genome, is a gene that enables selection of transformants during R&D.

II. Which agencies have oversight and why?

USDA GE corn is engineered with plant pest components.

EPA DNA codes for a pesticidal trait.

FDA GE corn will be used for food for humans and/or animals.

III. Developer responsibilities during R&D in contained systems (e.g., the laboratory and greenhouse)

R&D activities in contained systems are outside the regulatory authority of USDA/APHIS under the Plant Protection Act (PPA).

If the GE corn will be imported into the United States or transported across state lines, the developer must obtain an import or interstate shipment *notification/permit* from USDA/APHIS.

IV. Developer responsibilities prior to starting small-scale, non-contained field trials

Environmental release triggers USDA/APHIS regulatory requirements under the Plant Protection Act (PPA). The developer must obtain an *authorization for environmental release* from USDA/APHIS prior to starting field trials.

If the GE corn does not fit an existing categorical exclusion under NEPA,[1] USDA/APHIS will prepare the appropriate environmental analysis, either an *environmental assessment (EA) or environmental impact statement (EIS)*. Receipt of an authorization for an environmental release from USDA/APHIS is a prerequisite for moving the GE corn into the test field.

As the GE corn is for food use, the developer must obtain a *tolerance* or *tolerance exemption* for the residues of the pesticidal trait in the food from EPA under the Federal Food, Drug, and Cosmetic Act (FFDCA). Additionally, the developer may provide relevant scientific and technical information to FDA for their consideration and begin voluntary consultation about food safety and other FDA-related regulatory issues that may be associated with food from the GE corn.

V. Additional developer responsibilities prior to starting large-scale field trials

In addition to responsibilities triggered by small-scale field trials, the developer has reporting responsibilities if the field trial cumulative plot size is 10 acres or greater. The developer must obtain an *experimental use permit* (EUP) from EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

If the developer has not already done so, they may provide relevant scientific and technical information to FDA for the agency's consideration and begin voluntarily consultation about food safety and other FDA-related regulatory issues that may be associated with food from the GE corn. Similarly, if the developer has not already done so, they must obtain a *tolerance* or *tolerance exemption* from EPA.

VI. What must a developer do prior to commercialization?

The developer must ensure that all regulatory requirements have been met prior to commercialization of the GE corn.

The developer must receive either a *notification* or *permit* for importation, interstate movement, and environmental release, prior to commercialization. To be released from these requirements, a developer may petition USDA/APHIS for nonregulated status. During the review process, USDA/APHIS prepares a Plant Pest Risk Assessment and typically either an EA or an EIS to address the environmental impacts associated with the unconfined release of the GE corn. In most cases, nonregulated status is granted prior to commercialization. However it is not a prerequisite and commercialization may proceed under permit.

The developer must receive an EPA-issued *registration* and *tolerance or tolerance exemption* for the residues of the pesticidal trait in the food.

The developer is strongly encouraged to complete a voluntary consultation with FDA about food from the

[1] When a genetically engineered organism or products involves new species or organisms or novel modifications that potentially raise new issues, the authorization may not qualify for a categorical exclusion.

GE corn to help ensure that any food safety or other FDA-related regulatory issues[2] are resolved prior to marketing.

[2] As an example, food safety or other regulatory issues could involve the presence of an unapproved food additive in the resulting food product.

Case Study #2: Hypothetical, Genetically Engineered (GE) Plum with Pesticidal Properties

A fruit tree (fruit crop) used as food, is genetically engineered without a plant pest component to resist a fungus.

I. The product

Plum (*Prunus domestica*) is genetically engineered to express an enzyme that confers fungicidal properties. The gene encoding the protein was originally isolated from rice (*Oryza sativa*). The gene is controlled by a strong tissue-specific endogenous plum promoter. The promoter and gene are introduced into the tree genome using a biolistic approach. Also encoded on the linear DNA construct, and incorporated into the plum genome, is a selectable marker, which enables selection of transformants during R&D.

II. Which agencies have oversight and why?

EPA DNA codes for a pesticidal trait.

FDA GE plum will be used for food for humans and/or animals.

III. Developer responsibilities during R&D in contained systems (e.g., the laboratory and greenhouse)

Because there are no plant pest components associated with the GE plum tree, the developer has no reporting responsibilities to the regulatory agencies at this time. The developer is encouraged to confirm the *nonregulated status* with USDA/APHIS under PPA.

IV. Developer responsibilities prior to starting small-scale, non-contained field trials

Because the developer intends to introduce the GE plum into the food supply for humans and/or animals, the developer must obtain a *tolerance* or *tolerance exemption* for the residues of the pesticidal trait in the food from EPA under FFDCA. Additionally, the developer may provide relevant scientific and technical information to FDA for their consideration and begin voluntarily consultation about food safety and other FDA-related regulatory issues that may be associated with food from the GE plum tree.

V. Additional developer responsibilities prior to starting large-scale field trials

In addition to responsibilities triggered by small-scale field trials, the developer has reporting responsibilities if the field trial cumulative plot size is 10 acres or greater. The developer must obtain an experimental use permit (*EUP)* from EPA under FIFRA but does not need to obtain any authorizations from USDA/APHIS.

If the developer has not already done so, they may provide relevant scientific and technical information to FDA for their consideration and begin voluntary consultation about food safety and other FDA-related regulatory issues that may be associated with food from the GE plum tree. Similarly, if the developer has not already done so, they must obtain a *tolerance* or *tolerance exemption* from EPA.

VI. What must a developer do prior to commercialization?

The developer must ensure that all regulatory requirements have been met prior to commercialization of the GE plum tree.

The developer must receive an EPA-issued *registration* and *tolerance* or *tolerance exemption* for the residues of the pesticidal trait in the food.

The developer is strongly encouraged to complete a voluntary consultation with FDA about food from the GE plum tree to help ensure that any food safety or other FDA-related regulatory issues[3] are resolved prior to marketing.

[3] As an example, food safety or other regulatory issues could involve the presence of an unapproved food additive in the resulting food product.

Case Study #3: Hypothetical, Genetically Engineered (GE) Herbicide-tolerant Canola

A field crop, used as food for humans and/or animals, is genetically engineered with a plant pest component to tolerate an already registered herbicide. This particular herbicide has not previously been used on plants used for food for animals.

I. The product

Domesticated canola (*Brassica napus*) is genetically engineered to tolerate an herbicide by increasing the expression of a gene found in the canola genome using the constitutive 35S CaMV promoter. Extracted canola oils will be used for biodiesel production, and the remaining biomass processed into meal for food for animals and the animal or products of the animal may subsequently be consumed by humans. The 35S CaMV promoter and the canola gene are co-introduced into the plant using a biolistic approach. Because the canola gene confers resistance to an herbicide, no additional selectable marker is required. This particular herbicide, Herbicide X, is already registered by the EPA, but is not yet approved for use on animal food crops ("new food use"). In this scenario, a single developer produces both the herbicide-resistant canola and the herbicide.

II. Which agencies have oversight and why?

USDA The herbicide-tolerant plant is genetically engineered with plant pest components.

EPA Regulates the *new use* of the herbicide itself, not the genetic material used to engineer the plant.

FDA GE canola will be used for food for humans and/or animals.

III. Developer responsibilities during R&D in contained systems (e.g., the laboratory and greenhouse)

R&D activities in contained systems are outside the regulatory authority of USDA/APHIS under the Plant Protection Act (PPA).

If the GE canola will be imported into the United States or transported across state lines, the developer must obtain an import or interstate shipment *notification*/*permit* from USDA/APHIS.

IV. Developer responsibilities prior to starting small-scale, non-contained field trials

Environmental release triggers USDA/APHIS regulatory requirements under PPA. The developer must obtain an *authorization for environmental release* from USDA/APHIS.

Confined field trials[4] are typically categorically excluded from NEPA. They still have regulatory requirements under the PPA, including keeping field trials confined. But because this GE canola fits an existing categorical exclusion under NEPA, USDA/APHIS will not prepare either an EA or EIS.

Because the developer intends to introduce the GE canola into the food supply for humans and/or animals, the developer must obtain a *tolerance* or *tolerance exemption* for Herbicide X from EPA under FFDCA. Additionally, the developer may provide relevant scientific and technical information to FDA for their consideration and begin voluntary consultation about food safety and other FDA-related regulatory issues that may be associated with food from the GE canola.

V. Additional developer responsibilities prior to starting large-scale field trials

In addition to its responsibilities triggered by small-scale field trials, the developer has reporting responsibilities if the field trial cumulative plot size is 10 acres or greater. The developer must either amend the EPA registration of Herbicide X to allow for its use on GE canola or obtain from EPA a EUP for testing of Herbicide X on GE canola.

If the developer has not already done so, they may provide relevant scientific and technical information to FDA for their consideration and begin voluntarily consultation about food safety and other FDA-related regulatory issues that may be associated with food from the GE canola.

VI. What must a developer do prior to commercialization?

The developer must ensure that all regulatory requirements have been met prior to commercialization of the GE canola.

The developer must receive an authorization from USDA/APHIS for importation, interstate movement, and environmental release, prior to commercialization. To be released from these requirements, a developer may petition USDA/APHIS for nonregulated status. During the review process, USDA/APHIS prepares a Plant Pest Risk Assessment and typically either an EA or EIS to address the environmental impacts associated with the unconfined release of the GE canola. In most

[4] Confined field trials either stipulate specific measures or performance standards aimed at preventing the unintended release and persistence of the regulated organism in the environment.

cases, nonregulated status is granted prior to commercialization. However, it is not a prerequisite and commercialization may proceed under permit.

The developer must amend the EPA registration of Herbicide X to allow its use for human/animal food and obtain from EPA a *tolerance* or *tolerance* exemption for the Herbicide X.

The developer is strongly encouraged to complete a voluntary consultation with FDA about food from their GE canola to help ensure that any food safety or other FDA-related regulatory issues[5] are resolved prior to marketing.

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[5] As an example, food safety or other regulatory issues could involve the presence of an unapproved food additive in the resulting food product.

Case Study #4: Hypothetical, Genetically Engineered (GE) Rose

An ornamental plant is genetically engineered with a plant pest component to increase the production of a pigment in its petals.

I. The product

A rose (*Rosa* x *hybrida*) is genetically engineered to express a pigment from a black pansy (*Viola tricolor*). The transgene is controlled by the cauliflower mosaic virus-derived 35S promoter (CaMV) and introduced into the rose via *Agrobacterium*-mediated transformation. The purpose of the genetically engineered plant is to improve the quality of the product.

II. Which agencies have oversight and why?

USDA The plant is engineered with plant pest components, and is for ornamental use only.[6]

III. Developer responsibilities during R&D in contained systems (e.g., the laboratory and greenhouse)

R&D activities in contained systems are outside the regulatory authority of USDA/APHIS under the Plant Protection Act (PPA).

If the GE rose will be imported into the United States or transported across state lines, the developer must obtain an import or interstate shipment *authorization* from USDA/APHIS.

IV. Developer responsibilities prior to starting small-scale, non-contained field trials

Environmental release triggers USDA/APHIS regulatory requirements under PPA. The developer must obtain an *authorization for environmental release* to USDA/APHIS.

V. Additional developer responsibilities prior to starting large-scale field trials

If the GE rose does not fit an existing categorical exclusion under NEPA,[7] USDA/APHIS will prepare the appropriate environmental analysis, either an EA or EIS. The agency may use its discretion whether the EA or EIS should be prepared prior to or at the outset of large-scale field trial.

VI. What must a developer do prior to commercialization?

The developer must ensure that all regulatory requirements have been met prior to the commercialization of the GE rose.

The developer must receive an authorization for importation, interstate movement, and environmental release, prior to commercialization. To be released from these requirements, a developer may petition USDA/APHIS for nonregulated status. During the review process, USDA/APHIS prepares a Plant Pest Risk Assessment and typically either an EA or an EIS that would address environmental impacts associated with the unconfined release of the GE rose. In most cases, nonregulated status is granted prior to commercialization. However, it is not a prerequisite and commercialization may proceed under permit.

[6] In such cases, it is the responsibility of those marketing the rose in the US to ensure that the GE rose does not enter the food supply.

[7] When a genetically engineered organism or products involves new species or organisms or novel modifications that potentially raise new issues, the authorization may not qualify for a categorical exclusion.

Case Study #5: Hypothetical, Genetically Engineered (GE) Microbial Pesticide—Not a Plant Pest

A bacterium that is not considered a plant pest, is genetically engineered to enhance its pesticidal properties. The final product will be used on crops and is comprised of the GE bacterium.

I. The product

The bacterium *Bacillus thuringiensis (B. thuringiensis)* is genetically engineered to enhance the pesticidal properties of an endogenous protein. The gene encoding for that protein is controlled by an enhanced version of its own endogenous promoter. The gene, promoter, and selection marker (used to identify the transformed bacteria during R&D), are part of a vector that is transformed into *B. thuringiensis* via electroporation. The final product will be used on food crops and consists of the living *B. thuringiensis* and the pesticidal substance contained within the organism.

II. Which agencies have oversight and why?

EPA The product is a GE microbial pesticide.

III. Developer responsibilities during R&D in contained systems (e.g., the laboratory and greenhouse)

Under FIFRA, EPA regulations provide conditions to ensure the R&D is truly contained.

If the GE microbial pesticide will be imported into the United States, the developer must obtain a *pesticide notice of arrival* from EPA.

IV. Developer responsibilities prior to starting small-scale, non-contained field trials

If the GE microbial pesticide will be released into the environment for a field test (cumulative plot size less than 10 acres), the developer must submit a *biotechnology notification*[8] to EPA to determine whether or not a EUP is required under FIFRA. If the field trial cumulative plot size is 10 acres or greater see section V.

Because the developer intends to introduce crops treated with the GE microbial pesticide into the food supply for humans and/or animals, the developer must obtain a *tolerance* or *tolerance exemption* for the GE microbial pesticide from EPA under FFDCA.

V. Additional developer responsibilities prior to starting large-scale field trials

In addition to its responsibilities triggered by small-scale field trials, the developer has reporting responsibilities if the field trial cumulative plot size is 10 acres or greater. The developer must obtain a EUP from EPA under FIFRA, and if they have not already done so, a *tolerance* or *tolerance exemption* under FFDCA.

VI. What must a developer do prior to commercialization?

The developer must ensure that all regulatory requirements have been met prior to the commercialization of the GE microbial pesticide.

The developer must obtain an EPA-issued *registration* and *tolerance* or *tolerance exemption* for the GE microbial pesticide.

[8] *Biotechnology notifications* are required prior to experimental activities on small test plots to allow EPA to determine whether an *EUP* is required for microbial pesticides whose pesticidal properties have been imparted or enhanced by the introduction of genetic material that has been deliberately modified (40 CFR 172.45).

Case Study #6: Hypothetical, Genetically Engineered (GE) Microbial Pesticide—A Plant Pest

A phytopathogenic bacterium is genetically engineered to express a pesticidal substance that protects against insects. The genetically engineered living bacterium will be used to inoculate crops to increase their defense against insects.

I. The product

The bacterium *Clavibacter xyli* (*C. xyli*) is genetically engineered to express a delta-endotoxin protein used for controlling a pest, originally isolated from the bacterium *Bacillus thuringiensis*. The gene is controlled by a promoter derived from a bacterium. The gene, promoter, and selection marker (used to select transformed bacteria during R&D) are part of a vector that is transformed into *C. xyli* via electroporation. *C. xyli* is an endophytic bacterium, and GE *C. xyli* will be used to inoculate corn to induce insect resistance in the plant.

II. Which agencies have oversight and why?

USDA *C. xyli* is a plant pest.

EPA The product is a GE microbial pesticide.

III. Developer responsibilities during R&D in contained systems (e.g., the laboratory and greenhouse)

R&D activities in contained systems are outside the regulatory authority of USDA/APHIS under the Plant Protection Act (PPA).

However, under FIFRA, EPA regulations do provide conditions to ensure the R&D is truly *contained*.

If the GE microbial pesticide will be imported into the United States, the developer must obtain from USDA/APHIS an import *permit* and from EPA a *pesticide notice of arrival*.

If the GE microbial pesticide will be transported across state lines, the developer must obtain from USDA/APHIS an interstate shipment *permit*.

IV. Developer responsibilities prior to starting small-scale, non-contained field trials

Environmental release triggers USDA/APHIS regulatory requirements under PPA. The developer must obtain an *authorization for environmental release* from USDA/APHIS.

If the GE microbial pesticide does not fit an existing categorical exclusion under NEPA,[9] USDA/APHIS will prepare the appropriate environmental analysis, either an EA or EIS. The agency may use its discretion whether the EA or EIS should be prepared prior to or at the outset of small-scale field trial. Additionally, the developer must submit a *biotechnology notification*[10] to EPA to determine whether or not an experimental use permit (EUP) will be required under FIFRA.

Because the developer intends to introduce crops treated with the GE microbial pesticide into the food supply for humans and/or animals, the developer must obtain a *tolerance* or *tolerance exemption* for the GE microbial pesticide from EPA under FFDCA.

V. Additional developer responsibilities prior to beginning large-scale field trials

In addition to its responsibilities triggered by small-scale field trials, the developer has reporting responsibilities if the field trial cumulative plot size is 10 acres or greater. The developer must obtain a *EUP* from EPA under FIFRA.

If the developer has not already done so, they must obtain a *tolerance* or *tolerance exemption* from EPA.

VI. What must a developer do prior to commercialization?

The developer must ensure that all regulatory requirements have been met prior to commercialization of the GE microbial pesticide.

The developer must receive a *permit* for importation or interstate movement, a *pesticide notice of arrival* when imported, and an *authorization for environmental release*, prior to commercialization. To be released from these requirements, a developer may petition USDA/APHIS for nonregulated status. During the review process, USDA/APHIS prepares a Plant Pest Risk Assessment and typically either an EA or an EIS to address the environmental impacts associated with the unconfined release of the GE corn. In most cases, nonregulated status is granted prior to commercialization. Because *C. xyli* is a plant pest, USDA/APHIS might not grant non-regulated status. Instead, the commercial release of the *C. xyli*, would continue to be regulated under an *authorization*.

[9] When a genetically engineered organism or products involves new species or organisms or novel modifications that potentially raise new issues, the authorization may not qualify for a categorical exclusion.

[10] *Biotechnology notifications* are required prior to experimental activities on small test plots to allow EPA to determine whether an *EUP* is required for microbial pesticides whose pesticidal properties have been imparted or enhanced by the introduction of genetic material that has been deliberately modified (40 CFR 172.45).

The developer must obtain from EPA-issued *registration* and *tolerance* or *tolerance exemption* for the GE microbial pesticide.

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Case Study #7: Hypothetical, Genetically Engineered (GE) Algae for Biofuels

A unicellular alga is genetically engineered with a plant pest component to produce industrial oils for conversion into biofuels.

I. The product

The eukaryotic microalgae *Chlamydomonas reinhardtii* are genetically engineered to produce an enzyme that increases lipid biosynthesis. The extracted oils are later converted into biodiesel. The enzyme that increases lipid production was originally isolated from soybean (*Glycine max*). The soybean gene is controlled by the cauliflower mosaic virus-derived 35S promoter (CaMV). The plasmid encoding the enzyme, promoter, and selection marker is introduced into the algae through electroporation. *C. reinhardtii* will be cultivated in an open pond system. The remnants of the microalgae are intended for use as fish food.

II. Which agencies have oversight and why?

USDA The microalgae are engineered with a plant pest component (CaMV 35S promoter).

EPA The microalgae are engineered for industrial use with genes from outside the genus *Chamydomonas* and as such falls under rules implementing the Toxic Substances Control Act (TSCA).

FDA The microalgae will be used for animal food.

III. Developer responsibilities during R&D in contained systems (e.g., the laboratory and greenhouse)

R&D activities in contained systems are outside the regulatory authority of USDA/APHIS under the Plant Protection Act (PPA). However, under FIFRA, EPA regulations do provide conditions to ensure the R&D is truly *contained*. Under TSCA, EPA regulations exempt reporting provided certain conditions are met.[11]

IV. Developer responsibilities prior to starting small-scale, non-contained field trials

Environmental release triggers USDA/APHIS regulatory requirements under PPA. The developer must submit to USDA/APHIS an *authorization for environmental release*.

If the GE alga does not fit an existing categorical exclusion under NEPA,[12] USDA/APHIS will prepare the appropriate environmental analysis, either an EA or EIS. The EA or EIS would likely be required prior to the start of field trials in the open pond system.

Because the field trial is not contained, at least 60 days prior to the intended start of field trials in the open pond system the developer must submit a TSCA experimental release application (TERA) to and subsequently receive approval from the EPA.[13]

At this point, if not during the earlier stages of development, the developer may contact FDA about food safety and other FDA-related regulatory issues that may be associated with animal food derived from the algae.

V. Additional developer responsibilities prior to starting large-scale field trials

In addition to its responsibilities triggered by small-scale field trials, the developer has reporting responsibilities if the field trial cumulative plot size is greater than 10 acres. Under TSCA, developer obligations to EPA are the same for small- and large-scale field trials. Thus, the developer should have submitted a TERA and received approval from EPA prior to initial testing in the open pond system. Multi-year projects employing both small- and large-scale field trials may be included within a single TERA and reviewed as a unit. Separate, incremental TERAs may also be used, especially when the direction of work is dependent on findings from initial tests.

VI. What must a developer do prior to commercialization?

The developer must ensure that all regulatory requirements have been met prior to commercialization of the GE algae.

The developer must receive either an *authorization* for importation, interstate movement, and environmental release, prior to commercialization. To be released from these requirements, a developer may petition USDA/APHIS for nonregulated status. During the review process, USDA/APHIS prepares a Plant Pest Risk Assessment and typically either an EA or an EIS to address the environmental impacts associated with the unconfined release of the new microalgae. In most cases, nonregulated status is granted prior to commercialization. However it is not a prerequisite

[11] 40 CFR 725.235

[12] When a genetically engineered organism or products involves new species or organisms or novel modifications that potentially raise new issues, the authorization may not qualify for a categorical exclusion.

[13] If risk-associated issues are identified during the TERA review, EPA may extend period of review beyond 60 days.

and commercialization may proceed under permit. To avoid these requirements, a developer may petition USDA/APHIS for nonregulated status. During the review process, USDA/APHIS prepares a Plant Pest Risk Assessment and typically either an EA or an EIS that would address the environmental impacts associated with the unconfined release of the GE algae.

The developer is required to submit a microbial commercial activity notice (MCAN) to EPA under TSCA at least 90 days prior to initiation of manufacture, importation, or use. If risk-associated issues are identified during the MCAN review, EPA may negotiate or require limitations on manufacture and/or use. If no issues requiring regulation are found during MCAN review, the developer can commercialize, manufacture or use the microorganism in any manner they choose. Once a product has successfully cleared these reporting requirements and commercial manufacture and use begins, a developer can submit a *notice of commencement* to have the new microalgae listed on the TSCA Inventory.

The developer must also ensure that the related regulatory obligations to EPA under TSCA are met for all chemicals produced by the microalgae (if not currently listed on the Inventory).

The developer is strongly encouraged to consult with FDA about animal food uses of the microalgae to help ensure that any food safety or other FDA-related regulatory issues[14] are resolved prior to marketing.

[14] As an example, food safety or other regulatory issues could involve the presence of an unapproved food additive in the resulting food product.

Case Study #8: Hypothetical, Genetically Engineered (GE) Rabbit

An 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, for use downstream 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 allow expression of recombinant insulin protein in rabbit milk. The construct is microinjected into fertilized oocytes and the issuing embryos are transferred to the oviduct of a recipient. 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 and insulator sequences to minimize position effects at the locus of genome integration. Once a germline transgenic animal is identified as a founder animal, 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 coding sequence, integrated in the genome of the GE rabbit, is regulated as a new animal drug by the FDA Center for Veterinary Medicine (CVM) and the recombinant insulin purified from the GE rabbit milk is regulated as a human drug by the FDA Center for Drug Evaluation and Research (CDER).

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

The developer must initiate discussions with FDA/CVM once the founder animal(s) have been developed and the lineage is actively being characterized. FDA/CVM would open an investigational new animal drug file (INAD) into which the developer could submit data and information pertaining to this GE rabbit lineage.

The developer must obtain an Investigational New Drug (IND) exemption from FDA/CDER prior to clinical trial activities associated with the recombinant insulin product derived from this line of GE rabbits.

VI. What must a developer do prior to commercialization?

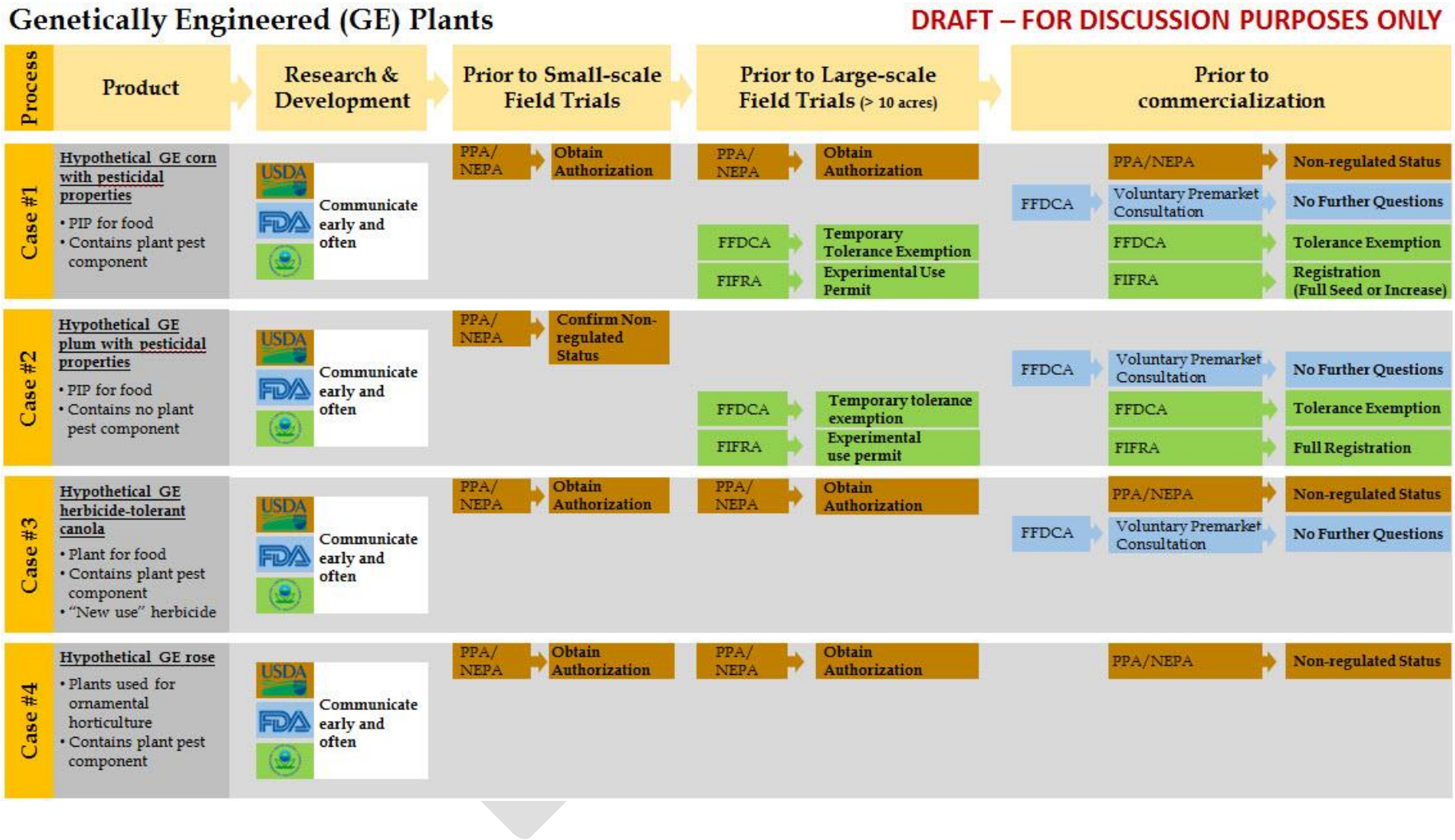
The developer must submit to FDA a new animal drug application (NADA) for the rDNA construct in the rabbit. The developer must also submit to FDA a new drug application (NDA) for the recombinant insulin product. In order to receive FDA approval, the developer must demonstrate that the GE rabbit meets the Federal Food, Drug, and Cosmetic Act's safety and effectiveness standards pertaining to animal and human drugs.

The developer must submit to FDA, under NEPA, an EA or a claim of categorical exclusion as part of its NADA or NDA submission.

The developer should keep both FDA/CVM and FDA/CDER apprised of activities related to the NADA and NDA in order to help ensure adequate communication between FDA/CVM and FDA/CDER related to areas of overlap, such as the milk from GE rabbits (bulk drug substance for FDA/CDER), and post-market reporting and commitments.

<u>Figure 1</u>: Graphic illustration of the eight case studies of hypothetical products from inception to commercialization

**Note that in many cases, products of biotechnology also have post market monitoring and reporting requirements that will apply but are not depicted here. More information on such requirements are available in relevant agency regulations and guidances.*



Genetically Engineered (GE) Microorganisms and Animals

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Process	Product	Research & Development	Prior to Small-scale Field Trials	Prior to Large-scale Field Trials or Pesticidal Intermediate	Prior to Commercialization
Case #5	**Hypothetical GE microbial pesticide, a plant pest** • Contains no plant pest component • To be used on food crops	USDA, FDA, EPA: Communicate early and often	PPA → Confirm Non-regulated Status FIFRA → Biotechnology Notification	FFDCA → Temporary Tolerance Exemption FIFRA → Exp. Use Permit	FIFRA → Tolerance Exemption; Full Registration
Case #6	**Hypothetical GE microbial pesticide, not a plant pest** • Contains plant pest component • GE bacterium increases herbivore resistance	USDA, FDA, EPA: Communicate early and often	PPA/NEPA → Obtain Authorization FIFRA → Biotechnology Notification	PPA/NEPA → Obtain Authorization FFDCA → Temporary Tolerance Exemption FIFRA → Exp. Use Permit	PPA/NEPA → Obtain Authorization FIFRA → Tolerance Exemption; Full Registration
Case #7	**Hypothetical GE algae for biofuels** • Contains plant pest component • Produces lipids for biodiesel production	USDA, FDA, EPA: Communicate early and often	PPA/NEPA → Obtain Authorization FFDCA → Consult FDA TSCA → TERA	PPA/NEPA → Obtain Authorization TSCA → TERA	PPA/NEPA → Non-regulated Status TSCA/MCAN → On the Inventory
Case #8	**Hypothetical GE rabbit** • Contains engineered rDNA construct (new animal drug) • Produces recombinant human insulin (new drug)	USDA, FDA, EPA: Communicate early and often	Investigational trials: FFDCA → Investigational New Animal Drug File; Investigational New Drug Exemption		Prior to commercialization: FFDCA → New Animal Drug Application (NADA); and New Drug Application (NDA) → NADA Approval; and NDA Approval

Additional Resources

Initiating dialog with the regulatory agencies (phone #, email, address, website)

USDA	Animal and Plant Health Inspection Service (APHIS)
	https://www.aphis.USDA-APHIS.gov/wps/portal/aphis/ourfocus/biotechnology/am-i-regulated
EPA	Office of Pesticide Programs (OPP)
	Office of Pollution Prevention and Toxics (OPPT)
FDA	Center for Biologics Evaluation and Research (CBER)
	Center for Drug Evaluation and Research (CDER)
	Center for Devices and Radiological Health (CDRH)
	Center for Food Safety and Applied Nutrition (CFSAN)
	Center for Veterinary Medicine (CVM)

Information on biotechnology from the agencies

USDA/APHIS	https://www.aphis.USDA-APHIS.gov/wps/portal/aphis/ourfocus/biotechnology
	https://www.aphis.USDA-APHIS.gov/biotechnology/downloads/notification_guidance_0311.pdf
EPA	http://www.epa.gov/pesticides/biopesticides
FDA	http://www.fda.gov/Food/FoodScienceResearch/GEPlants/default.htm;
	http://www.fda.gov/animalveterinary/developmentapprovalprocess/geneticengineering/geneticallyengineeredanimals/

For small entity biotechnology companies

If the developer is a small entity performing research on a minor crop, the developer might also consider contacting institutions, such as the IR-4 Project at Rutgers University (http://ir4-rutgers.edu/), to determine whether the institution can assist the developer navigate the regulatory process.