

Modernizing the Regulatory System for Biotechnology Products: Final Version of the 2017 Update to the Coordinated Framework for the Regulation of Biotechnology

A. Executive Summary

While the current Federal regulatory system for biotechnology products effectively protects health and the environment, advances in science and technology have altered the product landscape rapidly. In addition, the complexity of the current regulatory system with regard to biotechnology products can make it difficult for the public to understand how the safety of biotechnology products is evaluated and create challenges for small and mid-sized businesses navigating the regulatory process for these products.

To address these challenges, on July 2, 2015, the Executive Office of the President (EOP) issued a memorandum¹ (July 2015 EOP Memorandum) directing the primary agencies that regulate the products of biotechnology—the U.S. Environmental Protection Agency (EPA), the U.S. Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA)—to update the Coordinated Framework for the Regulation of Biotechnology (Coordinated Framework) by clarifying current roles and responsibilities, to develop a long-term strategy to ensure that the Federal biotechnology regulatory system is prepared for the future products of biotechnology, and to commission an expert analysis of the future landscape of biotechnology products to support these efforts. The goal of this work is to increase public confidence in the regulatory system and to prevent unnecessary barriers to future innovation and competitiveness.

This Update to the Coordinated Framework is a sequel to the 1986 Coordinated Framework for the Regulation of Biotechnology (the 1986 Coordinated Framework) and the 1992 Update to the Coordinated Framework and is intended to clarify the *current* roles and responsibilities of the primary agencies involved in the regulation of biotechnology products. The accompanying *National Strategy for Modernizing the Regulatory System for Biotechnology Products (Strategy)*, which was published in September 2016, identifies future steps to ensure the regulatory system addresses novel types of products developed through advances in science and technology appropriately. The Update to the Coordinated Framework and the *Strategy* were developed by the Biotechnology Working Group (Biotechnology WG) established by the July 2015 EOP Memorandum under the auspices of the Emerging Technologies Interagency Policy Coordination Committee. The July 2015 EOP Memorandum listed the following four tasks to be undertaken by the Biotechnology WG:

1. Clarify which biotechnology product areas are within the authority and responsibility of each agency;

¹ Memorandum for Heads of Food and Drug Administration, Environmental Protection Agency, and Department of Agriculture Regarding Modernizing the Regulatory System for Biotechnology Products, Executive Office of the President, July 2, 2015 (July 2015 EOP Memorandum). Available online at: https://www.whitehouse.gov/sites/default/files/microsites/ostp/modernizing_the_reg_system_for_biotech_products_memo_final.pdf.

2. Clarify the roles each agency plays for different product areas, particularly for those products that fall within the scope of multiple agencies, and how those roles relate to each other in the course of a regulatory assessment;
3. Clarify a standard mechanism for communication and, as appropriate, coordination among agencies, while they perform their respective regulatory functions, and for identifying agency designees responsible for this coordination function; and
4. Clarify the mechanism and timeline for regularly reviewing, and updating as appropriate, the Coordinated Framework to minimize delays, support innovation, protect health and the environment and promote the public trust in the regulatory systems for biotechnology products.

To accomplish the first task, this Update to the Coordinated Framework describes the types of biotechnology product areas regulated by the various components within each primary regulatory agency (*i.e.*, EPA, FDA, or USDA), organized by agency (see [Section D](#)). To accomplish the second task, this document provides a table of responsibilities, organized by biotechnology product area (see [Table 2](#)). The table describes the offices within each agency or agencies that may have regulatory responsibility for a given biotechnology product area, as well as relevant coordination across the agencies. To accomplish the third task, [Section E.2](#) of this document describes memoranda of understanding (MOU) among the agencies, and the types of products and information that are covered within the scope of each MOU. To accomplish the final task, [Section F](#) of this document discusses provisions for future review of the Coordinated Framework.

As part of this effort, the Biotechnology WG, under the auspices of the National Science and Technology Council (NSTC), published in the Federal Register a notice of request for information (RFI) and held three public meetings. Public comments received in response to the RFI and verbal public comments received at the three public meetings were reviewed in preparing the proposed Update to the Coordinated Framework (and in the development of the accompanying *Strategy*). A request for comment on the proposed version of the Update to the Coordinated Framework was published in the September 22, 2016 Federal Register.² The Biotechnology WG also reviewed all public comments received on the proposed Update to the Coordinated Framework as it finalized this Update to the Coordinated Framework.

B. Background

1. History of Federal Policy for the Regulation of Biotechnology Products

On June 26, 1986, the White House Office of Science and Technology Policy (OSTP) issued the Coordinated Framework for the Regulation of Biotechnology (the 1986 Coordinated Framework), which outlined a comprehensive Federal regulatory policy for ensuring the safety of biotechnology products. The 1986 Coordinated Framework noted that “the application of

² Federal Register 81 FR 65414.

traditional genetic modification techniques is relied upon broadly for enhanced characteristics of food (e.g., hybrid corn, selective breeding), manufactured food (e.g., bread, cheese, yogurt), waste disposal (e.g., bacterial sewage treatment), medicine (e.g., vaccines, hormones), pesticides (e.g., *Bacillus thuringiensis*) and other uses.”³ To ensure the safety of these types of products, Congress charged various Federal agencies with implementing an array of laws. A concise index of these laws was published in the Federal Register on November 14, 1985.⁴ The laws listed are product use-specific because they regulate certain product uses, such as for foods or as pesticides.

Recognizing its responsibility to address concerns raised about whether products resulting from the then “recently developed and newly emerging genetic manipulation techniques, such as recombinant DNA (rDNA), recombinant RNA (rRNA) and cell fusion” would pose greater risks than those achieved through traditional manipulation techniques, the Reagan Administration formed an interagency working group to address the matter.⁵ Upon examination of the existing laws to determine whether they might be used for the regulation of products developed using the emerging genetic manipulation techniques, the working group concluded that:

...[F]or the most part, these laws as currently implemented would address regulatory needs adequately. For certain microbial products, however, additional regulatory requirements, available under existing statutory authority, needed to be established.

The existing health and safety laws had the advantage that they could provide more immediate regulatory protection and certainty for the industry than possible with the implementation of new legislation. Moreover, there did not appear to be an alternative, unitary, statutory approach since the very broad spectrum of products obtained with genetic engineering cut across many product uses regulated by different agencies.⁶

The resulting 1986 Coordinated Framework explains the proper allocation and coordination of oversight responsibilities under the relevant statutes and among the relevant Federal agencies. The 1986 Coordinated Framework thus identified the regulatory agency (or agencies) that had oversight authority in each instance.⁷ The three primary regulatory agencies tasked with ensuring the safety of biotechnology products—the U.S. Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA)—each provided descriptions of their policies. The agency tasked with ensuring the safety and health of employees, the Occupational Safety and Health Administration within the

³Executive Office of the President. Office of Science and Technology Policy. Coordinated Framework for Regulation of Biotechnology, 51 FR 23302, at 23302-23303 (June 26, 1986) (1986 Coordinated Framework). Available online at: http://www.aphis.usda.gov/brs/fedregister/coordinated_framework.pdf.

⁴ Coordinated Framework for Regulation of Biotechnology, Establishment of the Biotechnology Science Coordinating Committee, Office of Science and Technology Policy; Notice, 50 FR 47174 (Nov. 14, 1985).

⁵ 1986 Coordinated Framework, 51 FR at 23302-23303.

⁶ 1986 Coordinated Framework, 51 FR at 23302-23303.

⁷ 1986 Coordinated Framework, 51 FR at 23302-23303.

U.S. Department of Labor, provided a description of how its existing regulations would ensure the safety and health of employees in the field of biotechnology. The 1986 Coordinated Framework also described the policies of the research agencies funding research into biotechnology processes and procedures at the time, the National Institutes of Health, the National Science Foundation, EPA, and USDA⁸. The document 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.⁹ In sum, when the 1986 Coordinated Framework was issued, it was acknowledged that it was “expected to evolve in accord with the experiences of the industry and the agencies, and, thus, modifications may need to be made through administrative or legislative actions.”¹⁰

On February 27, 1992, OSTP issued an update to the 1986 Coordinated Framework (the 1992 Update to the Coordinated Framework) that “set forth the proper basis for agencies’ exercise of oversight authority within the scope of discretion afforded by statute.”¹¹ It described a risk-based, scientifically sound basis for the oversight of activities that introduce biotechnology products into the environment. The 1992 Update to the Coordinated Framework reaffirmed that Federal oversight “focuses on the characteristics of the biotechnology product and the environment into which it is being introduced, not the process by which the product is created”¹² and clarified that “[e]xercise of oversight in the scope of discretion afforded by statute should be based on the risk posed by the introduction and should not turn on the fact that [a biotechnology product] has been modified by a particular process or technique.”¹³ Moreover, the 1992 Update to the Coordinated Framework stated that “[i]n order to ensure that limited federal oversight resources are applied where they will accomplish the greatest net beneficial protection of public health and the environment, oversight will be exercised only where the risk posed by the introduction is unreasonable.”¹⁴

⁸ In the “Proposal for a Coordinated Framework for Regulation of Biotechnology” which appeared in the December 31, 1984 Federal Register (49 FR 50356), the Federal Government recognized that a number of agencies, in addition to the EPA, FDA, and USDA, might have laws, regulations or guidelines that might be applicable to biotechnology products at some point in research, development, marketing, shipment, use, or disposal. The 1984 Proposal provided a matrix describing all the laws, regulations or guidelines that could potentially play a role. In addition to those agencies generally recognized as part of the Coordinated Framework, the matrix referenced Federal entities such as the Council on Environmental Quality, the U.S. Department of the Interior and the National Marine Fisheries Service. The Proposal noted that the matrix would be updated as appropriate, indicating that the Coordinated Framework was to be flexible in terms of which agencies might play a role in the regulation of biotechnology.

⁹ Executive Office of the President. Office of Science and Technology Policy. Exercise of Federal Oversight Within Scope of Statutory Authority: Planned Introductions of Biotechnology Products Into the Environment, 57 FR 6753 (Feb. 27, 1992) (1992 Update to the Coordinated Framework). Available online at: https://www.whitehouse.gov/sites/default/files/microsites/ostp/57_fed_reg_6753__1992.pdf.

¹⁰ 1986 Coordinated Framework, 51 FR at 23302-23303.

¹¹ 1992 Update to the Coordinated Framework, 57 FR at 6753.

¹² 1992 Update to the Coordinated Framework, 57 FR at 6753.

¹³ 1992 Update to the Coordinated Framework, 57 FR at 6753.

¹⁴ 1992 Update to the Coordinated Framework, 57 FR at 6753.

Consistent with the 1986 Coordinated Framework and the principles for regulation elaborated in both that document and the 1992 Update to the Coordinated Framework, and in accordance with their statutory authorities, the three primary regulatory agencies, EPA, FDA, and USDA, have developed their own agency-specific regulations, rules, and policy documents and updated them as necessary. This Update to the Coordinated Framework focuses on the activities of the three primary regulatory agencies.

2. Modernizing the Regulatory System for Biotechnology Products

Each of the primary Federal regulatory agencies with jurisdiction over the products of biotechnology has developed regulations and guidance documents to implement its authority under existing laws, resulting in a complex system for assessing and managing potential health and environmental risks posed by the products of biotechnology. While the current regulatory system for the products of biotechnology effectively protects health and the environment, in some cases unnecessary costs and burdens associated with uncertainty about agency jurisdiction, lack of predictability of timeframes for review, and other processes have arisen. These costs and burdens have limited the ability of technology developers, particularly those in small and mid-sized companies and in academic research institutions, to navigate the regulatory process and have limited the ability of the public to understand easily how the safety of these products is assured. Accordingly, the costs and burdens have the potential to hamper economic growth, innovation, and competitiveness.¹⁵

In addition, advances in science and technology have dramatically altered the biotechnology landscape since 1992, enabling the development of products not previously possible. An update of the Coordinated Framework documents of 1986 and 1992 was needed to facilitate the appropriate Federal oversight by the regulatory agencies, while continuing to provide a rigorous framework for advancing innovation and increasing transparency, coordination, efficiency, and predictability.¹⁶

On July 2, 2015, the Executive Office of the President (EOP) issued a memorandum (the July 2015 EOP Memorandum) directing the primary Federal agencies that have oversight responsibilities for biotechnology products¹⁷—EPA, FDA, and USDA—to update the Coordinated Framework to clarify the current roles and responsibilities of the agencies that

¹⁵ Memorandum for Heads of Food and Drug Administration, Environmental Protection Agency, and Department of Agriculture, Regarding Modernizing the Regulatory System for Biotechnology Products, Executive Office of the President, July 2, 2015 (July 2015 EOP Memorandum). Available online at: https://www.whitehouse.gov/sites/default/files/microsites/ostp/modernizing_the_reg_system_for_biotech_products_memo_final.pdf.

¹⁶ July 2015 EOP Memorandum

¹⁷ “Biotechnology products” in the July 2015 EOP Memorandum refers to products developed through genetic engineering or the targeted or in vitro manipulation of genetic information of organisms, including plants, animals, and microbes. It also covers some of the products produced by such plants, animals, and microbes or their derived products as determined by existing statutes and regulations. Products such as human drugs and medical devices are not the focus of the activities described in the memorandum. The July 2015 EOP Memorandum definition is not intended to supersede or amend any formal definitions found in existing regulations or to affect the unique scope of each law underlying the Coordinated Framework.

regulate the products of biotechnology, develop a long-term strategy to ensure that the Federal biotechnology regulatory system is prepared for the future products of biotechnology, and commission an independent, expert analysis of the future landscape of biotechnology products. These efforts are to build on the regulatory principles described in the 1986 Coordinated Framework and the 1992 Update to the Coordinated Framework. The tasks described in the July 2015 EOP Memorandum are intended to increase public confidence in the regulatory system and to prevent unnecessary barriers to future innovation and competitiveness by improving the transparency, coordination, predictability, and efficiency of the regulation of biotechnology products while continuing to protect health and the environment.

The memorandum established a Biotechnology Working Group (Biotechnology WG) under the Emerging Technologies Interagency Policy Coordination (ETIPC) Committee with representatives from the EOP, EPA, FDA, and USDA to implement the tasks from the memorandum. In addition, the memorandum stated that the update to the Coordinated Framework should clarify the current roles and responsibilities of the agencies that regulate biotechnology products by accomplishing the following four objectives:

- (i) clarifying which biotechnology product areas are within the authority and responsibility of each agency;
- (ii) clarifying the roles that each agency plays for different product areas, particularly for those product areas that fall within the responsibility of multiple agencies, and how those roles relate to each other in the course of a regulatory assessment;
- (iii) clarifying a standard mechanism for communication and, as appropriate, coordination among agencies, while they perform their respective regulatory functions, and for identifying agency designees responsible for this coordination function; and
- (iv) clarifying the mechanism and timeline for regularly reviewing, and updating as appropriate, the Coordinated Framework to minimize delays, support innovation, protect health and the environment and promote the public trust in the regulatory systems for biotechnology products.

To inform the proposed Update to the Coordinated Framework and other activities described in the July 2015 EOP Memorandum, the National Science and Technology Council (NSTC) published a notice of request for information (RFI) in the Federal Register to seek relevant data and information from stakeholders. In addition, OSTP, EPA, FDA, and USDA jointly held three public meetings, under the auspices of the NSTC, in different regions of the country to inform the public about their activities and seek public comments. Comments received in response to the RFI and transcripts of the public meetings, including comments received at the meetings, were placed in the public docket.¹⁸ The third public meeting also included breakout listening sessions, and a summary of individual input received during those sessions is available in the public docket. The Biotechnology WG reviewed all written comments submitted in response to the RFI, comments made at the three public meetings, and input from the breakout listening sessions in preparing a proposed Update to the Coordinated Framework. A general summary of the issues raised in those public comments is provided in [Appendix 1](#). The proposed Update to the

¹⁸ See <http://www.regulations.gov/#!docketDetail;D=FDA-2015-N-3403>

Coordinated Framework was released in September 2016 and the NSTC published a notice in the Federal Register seeking comment before finalizing the document. The Biotechnology WG reviewed all comments submitted in response to that notice in finalizing this Update to the Coordinated Framework. A general summary of the issues raised in those comments is provided in [Appendix 2](#).

C. Principles for the Regulation of the Products of Biotechnology

The following principles are drawn from the 1986 Coordinated Framework, the 1992 Update to the Coordinated Framework, Executive Orders 13563¹⁹ and 13610,²⁰ the 2011 *Principles for Regulation and Oversight of Emerging Technologies* memorandum,²¹ and the July 2015 EOP Memorandum. These principles continue to serve as guidance for the primary regulatory agencies that help ensure the safety of biotechnology products.

- Federal statutes and implementing regulations regulate products based on specific uses. This approach means that products with the same use are subject to the same types of oversight by the relevant regulatory agencies.
- Biotechnology products have applications in many areas, such as medicine, agriculture, energy, manufacturing, and environmental protection.
- The intended introduction of biotechnology products into the environment can be subject to Federal oversight under Federal statute(s) related to such products and their intended application.
- Each agency uses its existing statutory authorities and regulations to ensure the safety of the biotechnology products for their intended applications.
- Underlying statutes define the boundaries of the scope of oversight afforded to each regulatory agency.
- It is the characteristics of the biotechnology product, the environment into which it will be introduced, and the application of the product that determine its risk (or lack thereof).

¹⁹ On January 18, 2011, President Obama signed Executive Order 13563, Improving Regulation and Regulatory Review, which lays out principles that should guide Agency actions related to public participation, integration and innovation, flexibility of approaches, science, and retrospective analyses of existing laws. Exec. Order No. 13563, 76 FR 3821 (Jan. 18, 2011). Available online at: <https://www.whitehouse.gov/the-press-office/2011/01/18/executive-order-13563-improving-regulation-and-regulatory-review>

²⁰ On March 10, 2012, President Obama signed Executive Order 13610, Identifying and Reducing Regulatory Burdens, which lays out the steps that should be taken at the Agency level related to policy, public participation in retrospective reviews, priority setting, and accountability in order to modernize the U.S. regulatory system and to reduce unjustified regulatory burdens and costs. Exec. Order No. 13610, 77 FR 28467 (Mar. 10, 2012). Available online at:

https://www.whitehouse.gov/sites/default/files/docs/microsites/omb/eo_13610_identifying_and_reducing_regulatory_burdens.pdf

²¹ On March 11, 2011, the Office of Science and Technology Policy, Executive Office of the President, issued principles, consistent with Executive Order 13563, that should guide the development and implementation of policies for oversight of emerging technologies at the Agency level. Memorandum for the Heads of Executive Departments and Agencies, Principles for Regulation and Oversight of Emerging Technologies (Mar. 11, 2011). Available online at: <https://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/Principles-for-Regulation-and-Oversight-of-Emerging-Technologies-new.pdf>

- Exercise of agency oversight within the scope afforded by statutes should be commensurate with the risk posed by the introduction of the biotechnology product and should not turn on the fact that it was created or has been altered by a particular process or technique.
- To the extent permitted under relevant statutory provisions, following a risk-based approach to regulation, the regulatory system should distinguish between those biotechnology products that require a certain level of Federal oversight and those that do not.
- Because the overarching U.S. regulatory framework for biotechnology products relies on several different existing Federal laws, statutory nomenclature for certain actions may seem inconsistent; notwithstanding those seeming inconsistencies, the reviews conducted by each of the regulatory agencies are intended to be of comparable rigor to the extent allowed by law.
- The agencies endeavor to operate their programs in an integrated and coordinated fashion; together, they should cover the full range of plants, animals, and microorganisms derived from biotechnology.
- Future scientific developments will lead to further refinements of the Coordinated Framework. Experience with earlier basic scientific research has shown that as science progresses, regulatory regimens can be modified to reflect a more complete understanding of the potential risks involved. Refinements to the Coordinated Framework should consider any such updates to regulatory processes.

D. Roles and Responsibilities of the Primary Agencies that Regulate the Products of Biotechnology

This section describes the current statutory authorities and regulatory programs that EPA, FDA, and USDA use to help ensure the safety and, where applicable, the effectiveness of biotechnology products, including those products developed through genetic engineering (GE).¹⁵ Specifically, this section: (1) provides an overview of the statutory authorities used by each agency and the health and environmental protection goals each agency derives from those authorities (organized by agency), (2) identifies the product areas that fall within the statutory authorities and responsibilities of each agency (organized by agency), and (3) summarizes the role each agency plays in the regulation of biotechnology products (organized by product category). The 1986 Coordinated Framework, the 1992 Update to the Coordinated Framework, and this Update to the Coordinated Framework are based upon laws that govern the regulation of products and their uses, and are not triggered by the process by which products are made. Accordingly, the three primary Federal agencies employ a rational, scientific evaluation of products in providing oversight, taking into account how the processes used in the development or manufacture of the product may introduce, mitigate, or avoid risk.

The specific regulatory path (and relevant procedures) applicable to any product, including a biotechnology product, is dependent on the nature and characteristics of the product and its application. [Table 1](#) identifies the authorizing statutes and corresponding protection goals relevant to agencies' regulation of biotechnology products.

Table 1: Statutes and Protection Goals Related to EPA, FDA, and USDA for the Regulation of Biotechnology Products

<u>Agency</u>	<u>Statute</u>	<u>Protection Goal</u>
EPA	Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)	Prevent and eliminate unreasonable adverse effects on the environment <ul style="list-style-type: none"> • For environmental and occupational risks, this involves comparing economic, social, and environmental risks to human health and the environment and benefits associated with the pesticide use. • For dietary or residential human health effects, the sole standard is the “safety” of all the combined exposures to the pesticide and related compounds.
EPA	Federal Food, Drug, and Cosmetic (FD&C) Act	Ensure that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.
EPA	Toxic Substance Control Act (TSCA)	Prevent the manufacture, processing, distribution in commerce, use, or disposal of chemical substances, or any combination of such activities with such substances, from presenting an unreasonable risk of injury to health or the environment, including an unreasonable risk to a potentially exposed or susceptible population, without consideration of costs or other nonrisk factors.
FDA	Federal Food, Drug, and Cosmetic (FD&C) Act	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.
FDA	Public Health Service (PHS) Act	Ensure the safety, purity, and potency of biological products.
USDA	Animal Health Protection Act (AHPA)	Protect livestock from animal pest and disease risks.
USDA	Plant Protection Act (PPA)	Protect <i>agricultural plants</i> ²² and <i>agriculturally important natural resources</i> ²³ from <i>damage</i> ²⁴ caused by organisms that pose plant pest or noxious weed risks.
USDA	Federal Meat Inspection Act (FMIA)	Ensure that the United States’ commercial supply of meat, poultry, and egg products is safe, wholesome, and correctly labeled.
USDA	Poultry Products Inspection Act (PPIA)	Ensure that the United States’ commercial supply of meat, poultry, and egg products is safe, wholesome, and correctly labeled.

²² “Agricultural plants” are plants that have a function in agriculture, including crops, trees, pasture, and others.

²³ “Agriculturally important natural resources” are natural resources that have some function in or provide services to agriculture, *e.g.*, grazing land, flowing streams that provide water for agriculture, pollinators.

²⁴ “Damage” is biological, chemical, or physical damage, not damage due to market impacts, including those due to the presence of GE material (Damage is defined thus for the purposes of this document and the proposed revision of 7 C.F.R Part 340).

<u>Agency</u>	<u>Statute</u>	<u>Protection Goal</u>
USDA	Egg Products Inspection Act (EPIA)	Ensure that the United States' commercial supply of meat, poultry, and egg products is safe, wholesome, and correctly labeled.
USDA	Virus-Serum-Toxin Act (VSTA)	Ensure that veterinary biologics are pure, safe, potent and effective.

Biotechnology products that fall within the authorities and responsibilities of each agency are described in the subsections that follow. The information is organized by agency, and within each subsection by statute.

1. EPA

EPA is responsible for protecting human health and the environment. Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), EPA regulates pesticides. Under section 408 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), EPA establishes the amount of pesticide chemical residues that may be present in food. Under the Toxic Substances Control Act (TSCA) and regulations implementing that statute,²⁵ EPA currently regulates biotechnology products that are *new* organisms not specifically excluded by the statute (generally those regulated by other statutes). Below is a brief summary of the regulatory framework, including key legal provisions, applicable to the major biotechnology products that fall within EPA's jurisdiction.

a. Federal Insecticide, Fungicide, and Rodenticide Act

Under FIFRA, EPA regulates the sale, distribution, and use of all pesticides, including those produced through genetic engineering.²⁶ This group includes chemical pesticides, microorganisms, bio-chemicals, and plant-incorporated protectants (PIPs), a type of pesticide intended to be produced and used in living plants, when these are intended to be used as pesticides. Under FIFRA standards, EPA may register (*i.e.*, authorize an entity to sell or distribute a pesticide product with particular conditions of use) a pesticide if, when used in accordance with widespread and commonly recognized practice, it generally will not cause unreasonable adverse effects on the environment. FIFRA defines unreasonable adverse effects on the environment as: (1) any unreasonable adverse effects to man or the environment taking into account the economic, social and environmental costs and benefits of the use of a pesticide, or (2) a human dietary risk from residues that result from the use of a pesticide in or on any food inconsistent with the standard under section 408 of the FD&C Act.²⁷ A pesticide must thus meet two tests in order to be registered—the benefit of using the pesticide must outweigh the risk, and any residues in food (including food for animals) resulting from the use of the pesticide must meet the safety standard of section 408 of the FD&C Act. To support an application for a

²⁵ 40 C.F.R. Parts 700, 720, 721, 723, and 725.

²⁶ 7 U.S.C. § 136a(a).

²⁷ 7 U.S.C § 136(bb).

registration, EPA requires extensive scientific data and information on the potential health and environmental effects of a pesticide. The data and information allows EPA to evaluate whether, for instance, the pesticide could harm nontarget organisms and/or endangered species including humans, wildlife, and plants. Applicants for a registration must provide EPA data and information pertaining to, among other things, the identity, composition, potential adverse effects and environmental fate of each pesticide.²⁸ FIFRA provides EPA broad authority to establish or modify data needs and timing for registrations to achieve program and statutory objectives. Moreover, the Agency can issue data waivers, accept additional data or accept alternative approaches as appropriate. EPA reviews these data and information and establishes appropriate conditions of use.

EPA also regulates field testing by requiring Experimental Use Permits (EUPs). An EUP allows entities to generate data to support an application for registration, while ensuring sufficient regulatory controls are in place to prevent unreasonable adverse effects on health and the environment. EUPs authorize limited use of a pesticide on a limited number of acres under specific and controlled conditions to allow applicants to develop the necessary data. Under EPA regulations, experimental tests are presumed not to need an EUP when conducted on a cumulative total of no more than 10 acres of land or one surface acre of water per pest tested.²⁹ If the pesticide is a genetically engineered microorganism, the applicant must notify EPA when testing is less than 10 acres of land or one surface acre of water in order to confirm an EUP is not required. EPA will issue an EUP only when the test will not cause unreasonable adverse effects on the environment. If materials generated through the testing are to be used as food (including food for animals), any residues in those materials must meet the safety standard of section 408 of the FD&C Act.³⁰

Once a registration has been granted, registrants are obligated to comply with any obligations placed by EPA on the registration in connection with its distribution, sale and/or use. Registrants are also required to, among other things, pay annual maintenance fees for the registrations they have obtained;³¹ maintain certain records relating to pesticide production and distribution;³² permit entry by appropriately-credentialed EPA personnel to inspect their production facilities and/or allow such inspectors access to the records they are required to maintain;³³ submit any additional factual information regarding unreasonable adverse effects on the environment of the registered pesticide not previously submitted to EPA;³⁴ and submit any additional data EPA may

²⁸ 40 C.F.R. § 158.

²⁹ 40 C.F.R. § 172.3.

³⁰ 40 C.F.R. § 172.10(a); 21 U.S.C. § 346a(a)(1).

³¹ 7 U.S.C. § 136a-1(i).

³² 7 U.S.C. § 136f; 40 C.F.R. 169.

³³ 7 U.S.C §§ 136f(b); 136g(a).

³⁴ 7 U.S.C. § 136d(a)(2); 40 C.F.R. Part 159, Subpart D.

determine are needed to maintain in effect an existing registration of a pesticide.³⁵ Finally, FIFRA requires that EPA re-evaluate each registered pesticide at least every 15 years to determine whether the pesticide continues to meet the FIFRA standard for registration.³⁶

Additional information about EPA’s regulation can be obtained from EPA’s website at www.epa.gov.

Legal Statutes	FIFRA		FD&C Act	
	Sec. 2 – Pesticide definition Sec. 3 – Registration Sec. 5 – EUP		Sec. 408 – Tolerance(s)/ Tolerance exemption	
Product Sub-category	 Plant-Incorporated Protectants	 Microbial Pesticides	 Cell-Free Synthesis or Isolates	
Pre-market testing process	<ul style="list-style-type: none"> • Tolerance(s) / Tolerance exemption • EUP 	<ul style="list-style-type: none"> • Tolerance(s) / Tolerance exemption • Notification • EUP 	<ul style="list-style-type: none"> • Tolerance(s) / Tolerance exemption • EUP 	
Pre-market regulatory process	<ul style="list-style-type: none"> • Tolerance(s) / Tolerance exemption • Registration 	<ul style="list-style-type: none"> • Tolerance(s) / Tolerance exemption • Registration 	<ul style="list-style-type: none"> • Tolerance(s) / Tolerance exemption • Registration 	
EPA response	<ul style="list-style-type: none"> • Issue, or do not issue a registration • Issue, or do not issue a tolerance exemption 	<ul style="list-style-type: none"> • Issue, or do not issue a registration • Issue, or do not issue tolerance(s) or tolerance exemptions 	<ul style="list-style-type: none"> • Issue, or do not issue a registration • Issue, or do not issue tolerance(s) or tolerance exemptions 	

Figure 1. Overview of EPA Regulation of Biotechnology Products: Pesticides

b. Federal Food, Drug and Cosmetic Act (FD&C Act), section 408

EPA regulates the safety of any residual amounts of a pesticide or substances resulting from the use of a pesticide on a crop or food, including any metabolism or other degradation products of the pesticide (collectively referred to as “pesticide chemical residues”) that occur in or on food (including food for animals) under section 408 of the FD&C Act.³⁷ The FD&C Act makes it unlawful for food (including food for animals) to move in interstate commerce without a tolerance or tolerance exemption for any pesticide chemical residues it may contain.³⁸ EPA may establish a tolerance (maximum residue levels) or tolerance exemption that applies to both domestic and imported foods (for humans and animals) only if there is a reasonable certainty that no harm will result from aggregate exposure to residues of the pesticide in food for humans or animals, including all anticipated dietary exposures and all other exposures for which there is reliable information.³⁹ EPA establishes a tolerance exemption when it finds that, based on the nature of the chemical residues and the amounts that could remain in food after use of the

³⁵ 7 U.S.C. § 136a(c)(2)(B).

³⁶ 7 U.S.C. § 136a(g).

³⁷ 21 U.S.C. §§ 301 et seq.

³⁸ 21 U.S.C. §§ 346a(b)(2)(A)(i), (c)(2)(A)(i).

³⁹ 21 U.S.C. § 346a(b)(2)(A)(ii) or 346a(c)(2)(A)(ii).

pesticide, it does not need to set a maximum residue level to ensure the safety of the food. Tolerances or tolerance exemptions may be permanent or temporary, *e.g.*, issued for a limited time for pesticide chemical residues in materials resulting from field testing of a pesticide used as food (including food for animals). FDA enforces tolerances established by EPA for pesticide chemical residues in food (including food for animals); however, EPA retains the ability, whether in response to a petition or on its own initiative, to modify or revoke a tolerance.⁴⁰

c. Toxic Substances Control Act (TSCA) [Amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act]⁴¹

Under TSCA, EPA has oversight responsibilities for a wide range of commercial, industrial, and consumer applications of microbial biotechnology, when used to make products not specifically excluded from TSCA review. All “new chemical substances,” including intergeneric microorganisms, are subject to pre-manufacturing review under TSCA to prevent their manufacturing, processing, distribution in commerce, use, or disposal from presenting an unreasonable risk of injury to health or the environment, including to a potentially exposed or susceptible population, without consideration of costs or other nonrisk factors. EPA also has the authority to regulate existing chemical substances, including microorganisms, to prevent them from presenting an unreasonable risk of injury to health or the environment from their manufacture, processing, use, distribution in commerce, and disposal. Examples of TSCA applications include intergeneric microbial biotechnology products for biomass conversion for chemical production; microbial fuel cells; mining and resource extraction; building materials; waste remediation and pollution control; non-pesticidal agriculture applications such as bio-fertilizers; weather and climate modification; various consumer products and all other applications of intergeneric microbial biotechnology products not otherwise excluded under TSCA. TSCA specifically excludes food and food additives, drugs, cosmetics, medical devices, pesticides (but not pesticide intermediates), tobacco, nuclear material, and firearms from EPA jurisdiction.⁴² Microorganisms formed by the deliberate combination of genetic material from organisms classified in different taxonomic genera, including microorganisms constructed with synthetic genes that are not identical to DNA that would be derived from the same genus as the recipient, are considered “intergeneric” (*i.e.*, “new”) microorganisms, and so would be subject to the pre-manufacturing review provisions described above.

Under TSCA, manufacturers are required to report certain information to EPA before commencing the manufacture of intergeneric microorganisms that are not listed in the TSCA Inventory of Chemical Substances so that each may undergo a thorough risk assessment review to determine their safe use. EPA reviews information submitted in either: 1) a Microbial Commercial Activity Notice (MCAN), or 2) a TSCA Experimental Release Application (TERA) (The type of submission depends on whether the intergeneric microorganism is ready for

⁴⁰ 21 U.S.C. § 346a

⁴¹ 15 U.S.C. § 2601 et seq., as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act, P.L. No. 114-182 (June 22, 2016).

⁴² 15 U.S.C. § 2601(2)(B).

commercialization or still in the Research and Development phase). Reporting requirements and information used to conduct an MCAN or TERA risk assessment are outlined in 40 C.F.R. 725 and in specific guidance documents, including 1997's "*Points to Consider in the Preparation of TSCA Biotechnology Submissions for Microorganisms*" and "*Draft Algae Guidance for the Preparation of TSCA Biotechnology Submissions*." In addition to submitted data, EPA utilizes publicly available scientific information in its assessment of potential human health and environmental risks. The *Draft Algae Guidance for the Preparation of TSCA Biotechnology Submissions* document recognizes emerging biotechnological advancements and the resultant submissions received for review. It reflects the agency's effort to update all guidance to ensure adequate data and information accompanies all future TSCA notifications making use of these technologies. Additional new or revised guidance is contemplated for other relevant emerging technologies. If a submitter is unsure if they are regulated or require clarification of reporting requirements under TSCA, they are encouraged to contact EPA for a pre-notice consultation.⁴³

On June 22, 2016, TSCA was amended when President Obama signed into law the Frank R. Lautenberg Chemical Safety for the 21st Century Act.⁴⁴ While the amended TSCA does not address biotechnology specifically, it has implications for the biotechnology review process. TSCA now has a new requirement that EPA must make an affirmative finding on the safety of new chemical substances, including intergeneric organisms, before they are allowed into the marketplace. It also requires publication of a notice if EPA makes the determination that a new chemical substance, including intergeneric microorganisms, is not likely to present unreasonable risk of injury to health or the environment. EPA can still take a range of actions to address potential concerns including ban, limitations, and additional testing. [Figure 2](#) provides an overview of the relationship between legal statutes and regulated biotechnology product areas.

⁴³ <https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/forms/contact-us-about-regulation-biotechnology-under>

⁴⁴ Frank R. Lautenberg Chemical Safety for the 21st Century Act, P.L. No. 114-182 (June 22, 2016).

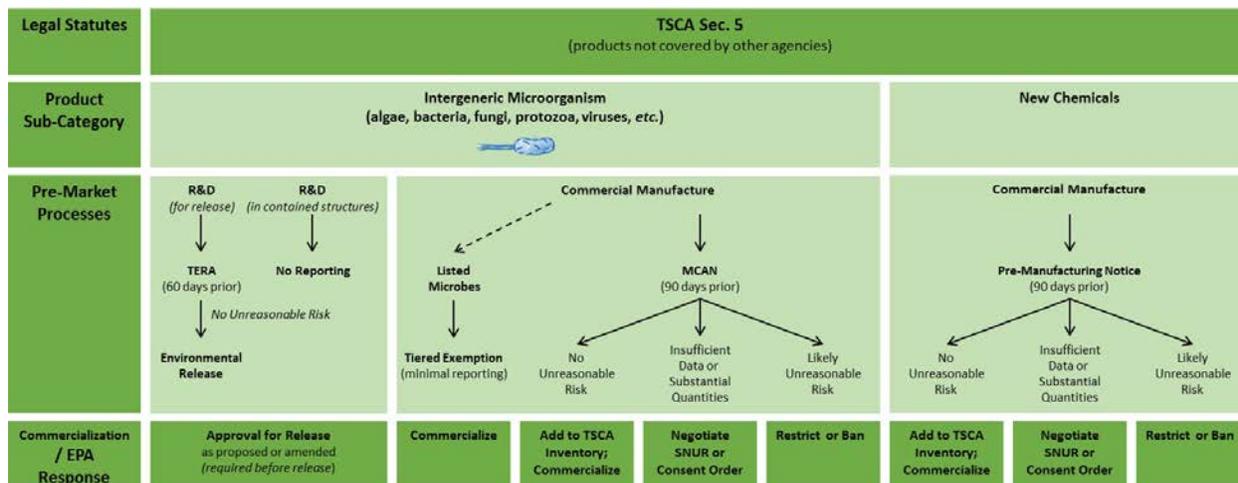


Figure 2. EPA Regulation of Biotechnology Products: TSCA

All uses not otherwise excluded by statute. Exclusions from TSCA are food, food additives, drugs, cosmetics, medical devices, pesticides (but not pesticide intermediates), tobacco, nuclear material, and firearms. See TSCA Section 3(2)(B), 15 U.S.C. § 2602(2)(B). Examples of those not excluded include biofertilizers, biofuel production, bioremediation, biosensors, and the production of detergent or other industrial enzymes.

2. FDA

FDA regulates a wide variety of products, including human and animal foods (including dietary supplements), cosmetics, human and veterinary drugs, human biological products, and medical devices (see Table 1). Below is a brief summary of the regulatory framework, including key legal provisions, applicable to the major biotechnology products that fall within FDA’s jurisdiction.

a. Human and Animal Foods Derived from GE Plants

FDA relies primarily on two sections of the FD&C Act to ensure the safety of foods (for humans and animals) and food ingredients, including those that are produced using genetic engineering:

(1) The adulteration provisions of section 402(a)(1) of the FD&C Act.⁴⁵ Under this authority, FDA has the power to remove a food from the market (as well as sanction those marketing the food) if the food bears or contains any poisonous or deleterious substance that may render it injurious to health (if the substance is an inherent constituent of the food, then the FDA may take

⁴⁵ 21 U.S.C. § 342(a)(1).

action if the quantity of the substance in the food would ordinarily render it injurious to health); and

(2) The food additive provisions of section 409 of the FD&C Act.⁴⁶ Under the FD&C Act, a substance that is intentionally added to food is a food additive, unless the substance is generally recognized as safe (GRAS) for the intended use or is otherwise excluded (*e.g.*, a pesticide, the safety of which is overseen by EPA, or a new animal drug, the safety of which is addressed by the new animal drug approval provisions of the FD&C Act).⁴⁷ Section 409 of the FD&C Act requires premarket approval of any food additive, regardless of the technique used to produce it or to add it to food.⁴⁸ Use of an unapproved food additive renders the food unsafe and subject to the adulteration provisions in section 402(a)(2)(C) of the FD&C Act.⁴⁹ The safety standard for food additives and GRAS substances is a reasonable certainty that the substance is not harmful under the conditions of its intended use.⁵⁰ Food additive approvals are published in the Federal Register. Once a food additive has been approved, there is a thirty-day period for submission of objections and requests for a hearing.⁵¹ Food additive approvals are also subject to the National Environmental Policy Act (NEPA)⁵² requirements.

In 1992, FDA issued a Statement of Policy: Foods Derived from New Plant Varieties, explaining how existing legal requirements apply to plant-derived food products developed using

⁴⁶ 21 U.S.C. § 348.

⁴⁷ 21 U.S.C. § 321(s).

⁴⁸ 21 U.S.C. § 348.

⁴⁹ 21 U.S.C. § 342(a)(2)(C).

⁵⁰ 21 C.F.R. §§ 170.3(i) and 570.3(i).

⁵¹ 21 U.S.C. § 348(f); 21 C.F.R. § 171.110.

⁵² The National Environmental Policy Act (NEPA), 42 U.S.C. § 4321 et seq., establishes a consistent process by which Federal agencies must consider the consequences of their proposed actions on the human environment prior to a decision. NEPA requires Federal agencies to prepare a detailed “environmental impact statement” (EIS) for all major Federal actions significantly affecting the quality of the human environment. 42 U.S.C. § 4332(2)(C). The Council on Environmental Quality (CEQ), an agency established by Congress in NEPA, has promulgated regulations that are applicable to Federal agencies in their compliance with NEPA. See 40 C.F.R. §§ 1500-1508. As well as specifying the process for preparation of an EIS, the CEQ regulations provide that Federal agencies may prepare an environmental assessment (EA) to determine whether a proposed action is likely to have a significant impact on the environment, thus triggering the need to prepare an EIS. 40 C.F.R. §§ 1501.3, 1501.4(e); 1508.9; 1508.13. CEQ regulations also provide that certain types of federal activities may be “categorically excluded” from NEPA review if the class of actions has no significant environmental effect, either individually or cumulatively, and there are no extraordinary circumstances in a given situation. 40 C.F.R. § 1508.4. Public involvement and the participation of state, tribal and local governments is an important component of the NEPA process. Each Federal department and agency is required to publish procedures, in consultation with CEQ, that identify how NEPA will be implemented for its typical actions. 40 C.F.R. § 1507.3. EPA’s decision making has generally been deemed to be ‘functionally equivalent’ to the NEPA process. See, *e.g.*, *Merrell v. Thomas*, 807 F.2d 776 (9th Cir. 1986). EPA does not therefore perform a NEPA analysis in addition to its environmental assessments of products under its purview.

biotechnology.⁵³ FDA subsequently established a voluntary premarket consultation process to help ensure that any safety or other regulatory issues associated with food from a new plant variety are resolved prior to commercial distribution.⁵⁴ These include the potential allergenicity and toxicity of any newly-introduced proteins in food from the plant, whether any newly-introduced substance in food from the plant requires premarket approval as a food additive, and whether levels of endogenous toxicants and important nutrients or anti-nutrients have been changed in a way that is relevant to food safety or nutrition.

In general, the safety and nutritional assessment information that FDA reviews includes: the name of the food developed using biotechnology and the crop from which it is derived; a description of the various applications or uses of the bioengineered food, including animal food uses; information concerning the sources, identities, and functions of introduced genetic material; information on the purpose or intended technical effect of the modification, and its expected effect on the composition or characteristic properties of the food; information concerning the identity and function of expression products encoded by the introduced genetic material, including an estimate of the concentration of any expression product in the bioengineered crop or food derived thereof; information regarding any known or suspected allergenicity and toxicity of expression products and the basis for concluding that foods containing the expression products can be safely consumed; information comparing the composition or characteristics of the bioengineered food to that of food derived from the parental variety or other commonly consumed varieties with special emphasis on important nutrients, and toxicants that occur naturally in the food; and information that addresses whether the potential for the bioengineered food to induce an allergic response has been altered by the genetic modification. When all safety and other regulatory issues are resolved, and the data and information logically support the conclusion that food from the new plant variety will be as safe as food from conventionally bred varieties, FDA concludes the consultation. FDA posts the results of completed consultations on its website. Although the consultation process is not legally required, to the best of FDA's knowledge, all GE food crops intended for marketing have been the subject of a consultation or other relevant premarket processes prior to marketing. The premarket consultation process provides for a rigorous food safety evaluation, and protects public health by helping firms ensure they are making market-entry decisions in compliance with the law.

In 2006, FDA published *Guidance to Industry: Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food*

⁵³ Department of Health and Human Services. Food and Drug Administration. Statement of Policy: Foods Derived from New Plant Varieties, 57 FR 22984 (May 29, 1992).

⁵⁴ See Consultation Procedures under FDA's 1992 Statement of Policy - Foods Derived from New Plant Varieties (June 1996; Revised October 1997). Available at: <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Biotechnology/ucm096126.htm>.

Use.⁵⁵ The guidance describes a program for early food safety evaluation of new non-pesticidal proteins in new plant varieties that are under development for food use. The program is designed to pro-actively address food safety concerns that might result if material from plants under development for food use is inadvertently present in the food supply at low levels prior to having been the subject of a completed food safety consultation with FDA. FDA anticipates that firms participating in this program will continue to interact with FDA using the agency's premarket consultation procedures (see Consultation Procedures under FDA's 1992 Statement of Policy - Foods Derived from New Plant Varieties⁵⁶ (June 1996; Revised October 1997),) which considers all relevant safety and regulatory questions associated with food from the variety.

As noted above, depending upon their characteristics, some substances added to food may require premarket authorization under the FD&C Act, such as those that are unapproved food or color additives. Regardless of whether premarket approval is required for a substance added to food, food manufacturers have an obligation to ensure that the foods they offer consumers are safe and in compliance with applicable legal requirements. Importantly, even after developers have completed any premarket processes with FDA, firms have an ongoing responsibility to ensure that the products they market are safe and lawful. If firms do not meet this obligation, FDA has authority under the FD&C Act to take enforcement action against unlawful foods and those marketing such foods. Enforcement actions can include warning letters, product recalls, seizures, injunctions, and criminal prosecution.

b. GE Animals

FDA regulates GE animals under the new animal drug provisions of the FD&C Act and FDA's implementing regulations. The definition of "drug" under section 201(g)(1)(C) of the FD&C Act includes "articles (other than food) intended to affect the structure or any function of the body of man or other animals."⁵⁷ The genetic material, or recombinant DNA (rDNA) construct, that is integrated into the DNA of an animal and is intended to affect the animal's structure or function meets this definition of a drug under the FD&C Act. The FD&C Act generally makes it unlawful to introduce unapproved new animal drugs into commerce.⁵⁸ Therefore, premarket approval requirements apply to GE animals before they are marketed, and potential environmental impacts, if any, must be examined prior to approval as required by the NEPA.^{59,60} The

⁵⁵ Available at:

<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Biotechnology/ucm096156.htm>

⁵⁶ Available at:

<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Biotechnology/ucm096126.htm>

⁵⁷ 21 U.S.C. § 321(g)(1)(C).

⁵⁸ See 21 U.S.C. §§ 331(a), 351(a)(5).

⁵⁹ 42 U.S.C. § 4321 et seq.

⁶⁰ As applicable, in accordance with NEPA, regulations issued by the Council on Environmental Quality (CEQ) (40 C.F.R. Parts 1500-1508), and FDA's Environmental Impact Considerations regulations under 21 C.F.R. Part 25, and

implementing regulations for new animal drugs are also applicable to GE animals, as appropriate to the particular submission.⁶¹ An exemption to the prohibition against interstate shipment of unapproved new animal drugs may be claimed when the drug is in investigational status and being shipped to experts qualified by scientific training and experience to investigate the safety and effectiveness of the investigational drug, if the requirements for the exemption set forth in 21 C.F.R. Part 511.1(b)(4) are met.

Within FDA, the Center for Veterinary Medicine (CVM) is responsible for evaluating the safety and effectiveness of the regulated article (the rDNA construct inserted in a specific site of the GE animal's genome). This includes the safety of any food derived from the GE animal as well as the safety of the article to the target animal. In addition, CVM evaluates whether the claims made by the sponsor are valid (*e.g.*, that the GE animal has a particular different fatty acid profile from its non-GE counterpart or that a GE animal produces the pharmaceutical it is supposed to produce). In general, FDA's review process has included these seven categories: *Product definition*: a broad statement characterizing the GE animal and the claim being made for the GE animal; *Molecular characterization of the construct*: a description of the rDNA construct or other genomic alteration and how they are produced; *Molecular characterization of the GE animal lineage*: a description of the method by which the rDNA construct or other genomic alteration was introduced into the animal and whether they are stably maintained over time; *Phenotypic characterization of the GE animal*: comprehensive data on the characteristics of the GE animal and its health; *Durability plan*: the sponsor's plan to demonstrate that the alteration will remain the same over time, and continue to have the same effect; *Environmental and food/feed safety*: the assessment of any environmental impacts, and for GE animals of food species, an assessment of the safety of food derived from those GE animals is safe to eat for humans and/or animals; and *Claim validation*: a demonstration that the GE animal has the characteristics that the developer says it has.

For GE animals producing substances to be used in or as drugs, biologics, or medical devices for use in humans, FDA's Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), or Center for Devices and Radiological Health (CDRH) has responsibility for reviewing those products that are produced by GE animals under their respective purview. Regarding GE animals, FDA intends to seek input from the public where there is significant public interest in an issue and FDA believes the public may have relevant data or information to contribute.⁶² After products are approved, FDA codifies the approval of new

to encourage public transparency, FDA has sought and considered public input in the agency's evaluation of the potential effects on the environment of the United States from an investigational use or approval of a new animal drug. However, confidentiality requirements generally prevent FDA from disclosing the existence of or releasing information contained in a new animal drug application file, including NEPA environmental documents, before approval of the new animal drug. In most cases, permission from the drug sponsor is required. See 21 C.F.R. §§ 20.61, 25.50(b) & 514.11.

⁶¹ 21 C.F.R. § 514.1(a).

⁶² Generally, confidentiality requirements prevent FDA from disclosing the existence of or releasing information contained in a new animal drug application file before approval of the new animal drug. In most cases, permission from the drug sponsor is required. See 21 C.F.R. § 514.11 & 21 C.F.R. § 20.61.

animal drugs, publishes a Federal Register notice when the approvals are codified, and posts on FDA's website a summary of the information on which the approval was based.

Once an application related to a GE animal is approved, sponsors have ongoing responsibilities including registration and drug listing, recordkeeping, filing supplements, and periodic reporting. Such post-approval monitoring is similar to the post-approval requirements for sponsors of conventional new animal drugs. Sponsors are required to register with the agency, and list all approvals related to GE animals they have produced, keep records of any additional information they develop related to the safety of the rDNA construct and the claim on which the approval was based. As with conventional drugs, if additional information shows that there are safety concerns, or if the GE animal no longer has the characteristics claimed for it, FDA can take steps to have the GE animal removed from the market.

After releasing a draft for public comment and considering public comments received, FDA issued a final guidance for industry on the regulation of GE animals in June 2015,⁶³ which clarifies FDA's approach to regulating GE animals and provides recommendations to help producers of GE animals meet their responsibilities under the law.

c. Human Drugs, Biological Products, and Medical Devices Derived from GE Sources

FDA regulates medical products, including human drugs, biological products, and medical devices, under the FD&C Act and the Public Health Service Act (PHS Act). 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. The FD&C Act establishes requirements for the development, manufacture, and marketing of drugs, including biological products, and medical devices to help ensure the safety and effectiveness of these products. Biological products are also subject to section 351 of the PHS Act, which contains licensing and other requirements to help ensure the safety, purity, and potency of these products.⁶⁴ Sponsors are required to obtain marketing authorization or premarket review from FDA to market most drugs, medical devices, and biological products, including combination products. As part of the review process, FDA evaluates the safety and effectiveness of the product.

As noted in the July 2015 EOP Memorandum, 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 and, therefore, is not discussed in detail in this document.

An overview of FDA's jurisdiction over food, medical, and other products is provided in Table 1, Figure 3, and Figure 4. Additional information about FDA's regulation can be obtained from FDA's website at www.fda.gov.

⁶³ Guidance for Industry: Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs (June 2015). Available online at: <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm113903.pdf>

⁶⁴ 42 U.S.C. § 262.

	†FOOD FOR HUMANS	†FOOD FOR ANIMALS	DRUGS FOR ANIMALS
Key Legal Provisions	FD&C Act Sec. 201 – Definitions of “food,” “food additive,” “color additive” Sec. 402 – Adulterated food Sec. 409 – Food additives Sec. 403 – Misbranded Food		FD&C Act Sec. 201 – Definition of “drug” and “new animal drug” Sec. 512 – NAD provisions (incl. INAD exemption) Sec. 501 – Adulterated drugs Sec. 502 – Misbranded drugs Sec. 402 – Adulterated food (contains unapproved NAD) Sec. 512(a) – Import tolerances
Pre-Market Processes	Food Additive Petition Color Additive Petition Premarket Consultation (new plant varieties) GRAS Notice NDI Notification Infant Formula Notification Food Contact Substance Notification	Food Additive Petition Color Additive Petition Premarket Consultation (new plant varieties) GRAS Notice	Investigational New Animal Drug (INAD) File New Animal Drug Application (NADA)
Pre-Market Regulatory Processes	Identify and complete any relevant premarket regulatory processes <i>(In some cases, participation in the relevant premarket regulatory processes may be voluntary.)</i> ↓ Assess safety, including safety of any food derived from animals, evaluate intended effect, and determine proper labeling ↓ NEPA Requirements, as applicable Evaluate environmental impacts of any potential approval (including food or color additive)		NADA Process ↓ Assess effectiveness and safety, including safety of any food derived from the animal ↓ Identify any related regulatory actions to be considered by other Centers (human drug, device, or biologic) ↓ NEPA Requirements, as applicable Evaluate environmental impacts of any investigational use or potential approval
FDA response	Approve/do not approve food or color additive petition, response letter to a voluntary consultation (new plant variety or GRAS); specific timeline after filing (NDI or Infant formula notification or Food contact substance notification)		Approve/do not approve NADA and any related actions (e.g., approval of NDA, BLA, device, or color or food additive by appropriate Center) (Post-approval requirements may apply)
Legend			
BLA = Biologics Licensing Application FD&C Act = Federal Food, Drug and Cosmetic Act GRAS = Generally Recognized as Safe	INAD = Investigational New Animal Drug NAD = New Animal Drug NDI = New Dietary Ingredient for dietary supplement use		NEPA = National Environmental Policy Act NADA = New Animal Drug Application † FDA-regulated foods

Figure 3. FDA Regulation Relevant to Biotechnology Products: Human and Animal Food and Animal Drugs

	DRUGS FOR HUMANS	BIOLOGICAL PRODUCTS FOR HUMANS	MEDICAL DEVICES FOR HUMANS
Key Legal Provisions	FD&C Act Sec. 201 – Definition of “new drug” Sec. 501 – Adulterated drugs Sec. 502 – Misbranded drugs Sec. 505 – New drug provisions PHS Act Sec. 351 – Definition of “biological product”; licensure requirements		FD&C Act Sec. 201 – Definition of “device” Sec. 501 – Adulterated devices Sec. 502 – Misbranded devices Sec. 510(k) – Premarket notification Sec. 513 – Classification of devices Sec. 515 – Premarket approval
Pre-Market Processes	New Drug Application Investigational New Drug Application Biologics License Application (for biological products)		Premarket Approval Application (or Humanitarian Device Exemption Application) Premarket Notification (510(k)) Investigational Device Exemption Application
Pre-Market Regulatory Processes	IND, NDA, and/or BLA Process ↓ Typical phases for clinical trials: <ul style="list-style-type: none"> • Phase 1 focusing on safety • Phase 2 focusing on effectiveness • Phase 3 involving large scale studies focusing on safety and effectiveness ↓ As part of NDA or BLA review, assess safety, effectiveness of drug or biological product and manufacturing process of biological product; the scope of IND review varies depending on the phase of the investigation ↓ NEPA Requirements, as applicable Evaluate environmental impacts of major agency actions ↓		PMA, HDE, 510(k), or IDE Process ↓ Assess safety, effectiveness of PMA device (HDE application similar to, but exempt from, effectiveness requirements of a PMA) Review substantial equivalence of 510(k) device Procedures to obtain approval to begin studies under an IDE depend on the risk level of the device ↓ NEPA Requirements, as applicable Evaluate environmental impacts of major agency actions ↓
FDA response	Approve/do not approve IND/NDA <i>(Post-market studies may apply with approval)</i>	Approve/do not approve IND/BLA <i>(Post-market studies may apply with approval)</i>	Approve/do not approve PMA (or HDE), IDE; Clear/NSE 510(k) <i>(Post-market studies may apply with approval)</i>
Legend			
BLA = Biologics Licensing Application FD&C Act = Federal Food, Drug and Cosmetic Act NSE = Not Substantially Equivalent		NDA = New Drug Application PMA = Premarket Approval IDE = Investigational Device Exemption	
		NEPA = National Environmental Policy Act HDE = Humanitarian Device Exemption IND = Investigational New Drug PHS Act = Public Health Service Act	

Figure 4. FDA Regulation Relevant to Biotechnology Products: Drugs, Biological Products, and Medical Devices for Human Use

3. USDA

a. APHIS

Within USDA, the Animal and Plant Health Inspection Service (APHIS) is responsible for protecting agriculture from pests and diseases. Under the Animal Health Protection Act (AHPA) and the Plant Protection Act (PPA), USDA regulates products of biotechnology that may pose a risk to agricultural plant and animal health.

USDA complies with provisions of NEPA, the Council on Environmental Quality’s (CEQ) regulations implementing NEPA,⁶⁵ and the USDA/APHIS’s NEPA-implementing regulations and procedures.⁶⁶ USDA prepares environmental documentation in full compliance with these provisions. Under these provisions, USDA is required to take a “hard look” at the significance

⁶⁵ 40 C.F.R. Parts 1500-1508.

⁶⁶ 7 C.F.R. Part 372.

of environmental impacts arising as a consequence of agency decisions, whether that is to issue an authorization for a regulated activity or to grant nonregulated status to a biotechnology product. Depending on the circumstances, APHIS prepares an Environmental Assessment (EA) or the much more comprehensive Environmental Impact Statement (EIS) prior to making decisions about issuing permits and on nonregulated status. The procedures for EAs and EISs give the public the opportunity to submit written comments on draft EAs and EISs in response to a Federal Register notice seeking comments from the public or attend public meetings (in person or virtually) where verbal or written comments may be entered into the record so that the agency can consider the information before publishing the final version of the EA or EIS. These environmental reviews help to inform the agency's decision making process.

APHIS announces its regulatory actions and the availability of related documents in the Federal Register. The public may provide comments regarding proposed actions online at [regulations.gov](http://www.regulations.gov), through conventional mail, and at various public meetings. The APHIS biotechnology website⁶⁷ offers access to a wide range of information, including documents open for comment, official documents, guidance for GE developers, status of applications for regulated activities, news, and upcoming events.

(1) Animal Health Protection Act (AHPA)

Under AHPA,⁶⁸ USDA has regulatory oversight over any products of biotechnology that are pests to or cause disease in livestock, or that could introduce pests to or cause disease in livestock with the goal to protect livestock. AHPA provides authority to prohibit or restrict the importation into the United States, transport across state lines within the United States, or dissemination of any pests to or disease-causing organisms in livestock populations, including animals that may present a risk of transmitting such pests or diseases. USDA would conduct an animal health risk assessment to determine if GE animals (including insects) presented a risk to livestock health. GE animals (including insects) would be subject to import or transport restrictions if there is a risk to animal health. Under AHPA, regulations are limited to animal health of livestock (horses, cattle, bison, sheep, goats, swine, cervids, poultry, and other farm-raised animals, including farm-raised fish). GE insects are regulated under this section similar to non-GE insects on their ability to contain any contagious, infectious, or communicable disease of livestock.

(2) Plant Protection Act (PPA)

Under PPA,⁶⁹ USDA has regulatory oversight over products of biotechnology deemed plant pests and noxious weeds with a goal of protecting plants and plant products.⁷⁰ A GE organism is

⁶⁷ See http://www.aphis.usda.gov/biotechnology/brs_main.shtml

⁶⁸ 7 U.S.C. §§ 8301 et seq.

⁶⁹ 7 U.S.C. §§ 7701 et seq.

⁷⁰ The current biotech regulations, 7 C.F.R. Part 340, which were codified prior to the Plant Protection Act, only invoke the Plant Pest Authority under the PPA. A separate regulation enforced by USDA, 7 C.F.R. Part 360, does

considered a regulated article if the donor organism, recipient organism, vector, or vector agent used in engineering the organism belongs to one of the taxa listed in 7 C.F.R. Section 340.2 and is also considered a plant pest. A GE organism is also regulated when APHIS has reason to believe that the GE organism may be a plant pest. APHIS oversight encompasses bacteria, fungi, viruses, and invertebrate animals such as insects, arachnids, and nematodes. A GE organism is no longer subject to the plant pest provisions of PPA or to regulatory requirements at 7 C.F.R. Part 340 when APHIS conducts a plant pest risk assessment and determines that the organism is unlikely to pose a plant pest risk. Required data and information to conduct a plant pest risk assessment and on which to base a determination of nonregulated status is provided in 7 C.F.R. 340.6(c) and in further guidance on APHIS' web page.⁷¹ In addition, APHIS utilizes publicly available scientific information in its assessment of potential plant health risks. Once APHIS makes a determination of nonregulated status, there are no post-market requirements for the product's release. APHIS may also issue an authorization, specifically a permit, for the commercialization of a product that meets the regulatory definition. In these cases, APHIS would maintain post-market oversight in the form of specific requirements on the introduction of the product and through its compliance and inspection programs. Figure 5 details the relationship between legal statutes, regulated GE product areas, and required documentation prior to and following commercial release. When a GE plant is capable of causing injury or damage as a noxious weed under the PPA, APHIS regulations at 7 C.F.R. Part 360 may be considered in evaluating those risks relative to injury and damage that may be caused by the unmodified plant. If a developer is unsure, or wants assurance, that it has interpreted the regulations correctly when reaching a self-determined decision as to whether their GE organism meets the definition of a regulated article as described above, prior to proceeding with an introduction, it may seek a confirmation of regulatory status of the GE organism from APHIS by providing certain information to the Agency under its "Am I Regulated" process.⁷²

In exercising its authority, APHIS engages the public in several ways and at several points in its decision making process. APHIS may engage the public on certain regulated activities associated with the issuance of a permit. APHIS prepares an EA and, on very rare occasions may prepare an EIS, for some permit applications. Permits requiring an EA or EIS include products that are themselves plant pests, for which there is reason to believe may be a plant pest, or may present an impact to the environment for which a finding of no significant impact cannot be made because the species or genetic modification has not been seen in the past, *e.g.*, pharmaceutical, industrial and phytoremediation products, certain trees and grasses, and invasive or noxious weeds. After developing an EA and a finding of no significant impact (FONSI),

include noxious weed protection applicable to both GE and non GE plants. Under the regulations at 7 C.F.R. Part 340, USDA/APHIS has authority to regulate the importation, interstate movement, or release into the environment of certain GE organisms. The GE organisms regulated by USDA are those produced using plant organisms, DNA from plant pest organisms, or those for which there is otherwise a reason to believe that the organism is a plant pest.

⁷¹ Information for submitting a petition for nonregulated status can be found in 7 C.F.R. Part 340 §§ 6(c) and at <https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/permits-notifications-petitions/petitions>.

⁷² Information on submitting a regulatory confirmation inquiry can be found on APHIS web page at <https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated>

APHIS publishes a notice in the Federal Register announcing availability of these documents for a 30-day public comment period. If no information is received that warrants substantial changes to APHIS's analysis or the need for an EIS, APHIS will issue the authorization for the regulated activity and announce its decision through a stakeholder message and an announcement on its website. No further Federal Register notice is published announcing the final regulatory decision. If an EIS is necessary, APHIS will follow the NEPA procedure at 40 C.F.R. Part 1500.⁷³

On March 6, 2012, APHIS implemented petition process improvements, including enhancements to the way it solicits public input on petitions for nonregulated status.⁷⁴ APHIS now has two opportunities for public involvement when it conducts an EA. First, when APHIS deems a petition complete, the petition is made available for public comment for 60 days before preparation of an EA and Plant Pest Risk Assessment (PPRA). The availability of the petition for public comment is announced in a Federal Register notice. This first comment opportunity is for the public to raise issues regarding the petition itself and to provide input for APHIS to consider as it develops the EA and PPRA. If APHIS determines that an EA provides ample analysis, it develops an EA and PPRA and publishes a second Federal Register notice announcing availability of those documents for public comment opportunity. This second notice may also announce public meetings if the agency believes they would be beneficial to gather public input on the analyses. APHIS may also decide, based on the public's input and other factors, that an EIS is necessary, in which case APHIS will complete the NEPA EIS process in accordance with CEQ regulations and APHIS's NEPA implementing regulations. At this point, the public may have as many as three additional opportunities to provide input into the decision making process. APHIS may also conduct public meetings (in person or virtually) to accept oral and written comment on its analyses.

(3) Virus-Serum-Toxin Act (VSTA)

Under VSTA,⁷⁵ USDA has regulatory oversight over products of biotechnology that are included in veterinary biologics. The VSTA provides authority to ensure that veterinary biologics are pure, safe, potent and effective. USDA regulates the manufacturing and distribution of veterinary biological products used to prevent, diagnose, and treat animal diseases. Products of biotechnology that are used in veterinary biologics are subject to these regulations, and the final biologic is evaluated for purity, safety, potency, and effectiveness. All veterinary biologics, including products of biotechnology, which have received a license are subject to continued oversight. In addition to regular inspection of the manufacturing facility and testing requirements, manufacturers are required to immediately (within 72 hours) report to USDA any time there are indications that raise questions regarding the purity, safety, potency or efficacy of a product, or if it appears there may be a problem regarding the preparation, testing, or distribution of a product.

⁷³ See https://ceq.doe.gov/ceq_regulations/Council_on_Environmental_Quality_Regulations.pdf.

⁷⁴ See https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/permits-notifications-petitions/petitions/ct_pet_proc_imp.

⁷⁵ 21 U.S.C. §§ 151 et seq.

	PRODUCTS WITH PLANT PEST COMPONENTS	GE ANIMALS	PRODUCTS WITH ANIMAL PATHOGENS	
Legal Statutes	PPA 7 CFR Part 340	AHPA	21 USC 151-159 9 CFR Parts 101-124	
Product Sub-Category	GE Plants, Microorganisms, and Invertebrates	GE Animals	Veterinary Biologics	
Pre-Market Processes	<p>Application for Authorization (Permit or Notification) <i>(for importation, interstate movement, or environmental release)</i> <i>(Post-issuance oversight continues for the duration of the authorization and would apply to authorization issued for commercial production)</i></p> <p>↓</p> <p>NEPA Analysis (Categorical Exemption, Environmental Assessment, or Environmental Impact Statement)</p> <p>↓</p> <p>Issue Importation, Interstate Movement, or Environmental Release Authorization</p>	<p>Petition for Nonregulated Status <i>(for deregulation)</i> <i>(Post-market requirements do not apply if product is granted nonregulated status)</i></p> <p>↓</p> <p>NEPA Analysis (Environmental Assessment or Environmental Impact Statement; Plant Pest Risk Assessment)</p>	<p>Permit <i>(if applicable after risk assessment)</i></p>	<p>Application for Authorization (Permit or Notification) <i>(for importation or interstate movement)</i></p> <p>↓</p> <p>NEPA Analysis (Environmental Assessment or Environmental Impact Statement)</p> <p>↓ If finding of no significant impact</p> <p>Environmental Release</p>
USDA / APHIS Response	On-going Regulatory Oversight	Deregulation or Continued Regulation	Coordinate with FDA	On-going Regulatory Oversight

Figure 5. USDA/APHIS Regulation of Biotechnology Products

b. FSIS

The Food Safety and Inspection Service (FSIS) is the public health agency in USDA that is responsible for ensuring that the United States' commercial supply of meat, poultry, egg products, and fish of the Order Siluriformes is safe, wholesome, and correctly labeled. Under the Federal Meat Inspection Act (FMIA), Poultry Products Inspection Act (PPIA), and Egg Products Inspection Act (EPIA), FSIS inspects all meat, poultry, and processed egg products in interstate commerce.

FDA will inform FSIS of any reviews of the safety of meat, poultry, eggs, or fish of the Order Siluriformes from a GE animal (livestock) intended to be used for human consumption, as well as the safety of any substances added to such meat, poultry, eggs, or fish of the Order Siluriformes as a result of the genetic engineering. FDA oversees the safety of substances added to meat products, poultry products, egg products, and/or fish of the Order Siluriformes using its authority under the FD&C Act, while FSIS considers whether use of such substances in meat, poultry, egg, and/or fish of the Order Siluriformes products is suitable under FMIA, PPIA, and EPIA.⁷⁶

FSIS would communicate to the public and stakeholders through public meetings and regularly held consumer and industry meetings any determinations made regarding a GE animal

⁷⁶See 225-00-2000 Amendment 1, Memorandum of Understanding between the U.S. Department of Agriculture Food Safety and Inspection Service and the U.S. Department of Health and Human Services Food and Drug Administration. Available online at: <http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm441552.htm>

(livestock) or a substance added to meat, poultry, eggs, or fish of the Order Siluriformes as a result of genetic engineering. Additionally, FSIS will utilize askFSIS, a Web-based computer application, designed to help more effectively respond to technical and policy-related questions, including determinations regarding GE product, from inspection program personnel, industry, consumers, other stakeholders, and the public.

	FOOD		
Legal Statutes	FMIA Sec. 601(m) – adulterated Sec. 601(n) – misbranded Sec. 601(j) – meat food product	PPIA Sec. 453(e) – poultry Sec. 453(f) – poultry food product Sec. 453(g) – adulterated Sec. 453(h) – misbranded	EPIA Sec. 1033(a) – adulterated Sec. 1033(f) – egg product Sec. 1033(l) – misbranded
Product Sub-Category	Meat Products	Poultry Products	Egg Products
Pre-Market Processes	Evaluate the suitability of the use of substances in meat under the Joint FDA and FSIS ingredient approval process Prior approval of meat product labels	Evaluate the suitability of the use of substances in poultry under the Joint FDA and FSIS ingredient approval process Prior approval of poultry product labels	Evaluate the suitability of the use of substances in egg products under the Joint FDA and FSIS ingredient approval process Prior approval of egg product labels
	Assess suitability of food additives, food contact substances, and GRAS notifications Assess compliance of labels with FSIS requirements		
USDA / FSIS Response	Notify FDA of FSIS's suitability findings regarding the use of substances considered by FDA in food additive petitions, food contact substance notifications, and GRAS notifications that have intended uses in meat, poultry, and egg products Approve labels that are in compliance with FSIS requirements, reject labels that are not in compliance Provide Federal establishments with a notification of FSIS's assessment and reasons for rejection, if applicable		

Figure 6. USDA/FSIS Regulation of Biotechnology Products

4. Oversight of Biotechnology Products and Relevant Coordination across EPA, FDA, and USDA

Table 2 below summarizes current responsibilities and the relevant coordination across EPA, FDA, and USDA for the regulatory oversight of biotechnology products. The table identifies the responsible agency or agencies for different products and their applications. The information is organized as a matrix of types of source organism or culture (*e.g.*, plant, animal, microbe, cultured cell, cell-free synthesis) along the horizontal axis and product areas along the vertical axis. The accompanying *Strategy* identifies future steps the agencies intend to take.

Table 2: Oversight of Biotechnology Products and Relevant Coordination across EPA, FDA, and USDA

This table summarizes current responsibilities and the relevant coordination across EPA, FDA, and USDA for the regulatory oversight of biotechnology products, based on the scope of each agency's current authorities.⁷⁷ While the information in this table is intended to be as comprehensive and accurate as possible, it should not be construed to impair or otherwise affect the agency mission as established by law for each agency or the authority granted by law to each agency or the head thereof. Also, the information in the table should not be interpreted as a guarantee that specific products in any of the areas specified have been in the past, or will be in the future, determined to be safe. The table does not specify the applicable regulatory requirements or procedures, which may vary depending on the product. The table does not identify additional government agencies and associated requirements that may be relevant to products imported into the United States for marketing or investigation. Products imported into the United States must meet all applicable requirements, including any import certification and permit requirements. Also note that the inclusion of a product area in this table does not indicate the existence of commercially available products or endorsement of the development of such products by the Federal government. In Section G, this document provides some case study examples that illustrate how the agencies use some of these authorities. Note also that potential future applications of regulatory authority under a statute of the Coordinated Framework to ensure a class of products is adequately regulated may not be reflected in this Table.

⁷⁷ The 1986 Coordinated Framework (in Chart I at 51 FR 23304) identifies a “lead agency” among the agencies responsible for regulation of a specific product category or use. This Update to the Coordinated Framework does not identify lead agencies because the concept caused confusion and was mistakenly interpreted. For example, stakeholders have incorrectly understood the lead agency as being responsible for making all relevant regulatory decisions, guiding developers from one agency to another, or being the conduit through which communications between developers and regulatory agencies flow. Further, this concept may incorrectly lead some to believe that one agency would withhold an authorization until other agencies had completed their regulatory work. Notwithstanding the 1986 concept of a lead agency, these agencies have developed a successful network of coordination and communication that can assist developers in navigating the Coordinated Framework. For discussion of the types of coordination and communication that occur between EPA, FDA and USDA, see section E of this document.

Agency Acronyms

<u>EPA</u>	<u>Environmental Protection Agency</u>
OPP	Office of Pesticide Programs (EPA)
OPPT	Office of Pollution Prevention and Toxics (EPA)

<u>FDA</u>	<u>Food and Drug Administration</u>
CBER	Center for Biologics Evaluation and Research (FDA)
CDER	Center for Drug Evaluation and Research (FDA)
CDRH	Center for Devices and Radiological Health (FDA)
CFSAN	Center for Food Safety and Applied Nutrition (FDA)
CVM	Center for Veterinary Medicine (FDA)

<u>USDA</u>	<u>Department of Agriculture</u>
APHIS	Animal and Plant Health Inspection Service (USDA)
VS	Veterinary Services (USDA/APHIS)
CVB	Center for Veterinary Biologics (USDA/APHIS/VS)
FSIS	Food Safety and Inspection Service (USDA/FSIS)

Oversight of biotechnology products and relevant coordination across EPA, FDA, and USDA

Product Area	Source Organism or Culture		
	<i>Genetically Engineered Plant</i>	<i>Genetically Engineered Animal</i>	<i>Genetically Engineered Microbe or Cultured Cell</i>
Food for humans	<u>USDA/APHIS</u> ⁷⁸ If plant poses a plant pest risk <u>FDA/CFSAN</u> ⁷⁹ <u>EPA/OPP</u> If plant-incorporated protectant is produced by plant, EPA/OPP regulates the pesticide substance and related genetic material for human and environmental safety, including the safety of dietary exposures to pesticide residues in human and animal food.	<u>FDA/CVM</u> ⁸⁰ <u>USDA/APHIS</u> If animal poses a plant pest risk <u>USDA/APHIS/VS</u> If animal poses health risk to livestock ⁸¹ <u>FDA/CFSAN</u> ⁸² <u>USDA/FSIS</u> ⁸³	<u>FDA/CFSAN</u> <u>USDA/FSIS</u>

⁷⁸ USDA/APHIS oversees the importation, interstate movement, and environmental release of the plants (that pose a plant pest risk) that are used for food purposes. USDA/APHIS does not regulate activities in confined facilities such as laboratories and greenhouses.

⁷⁹ FDA has a voluntary food safety and regulatory consultation process for human and/or animal foods derived from genetically engineered plant varieties to be used in the food supply and recommends that developers of such products partake in the consultation process early in the development process (see <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Biotechnology/ucm096095.htm>). Particular uses of foods (including food substances) may be subject to certain premarket requirements; the fact that a food or food substance does or does not come from a genetically engineered plant has no bearing on those requirements. FDA also conducts a program that is focused on the early food safety evaluation of new non-pesticidal proteins produced by new plant varieties under development for food use. The program is designed to pro-actively address food safety concerns that might result in the event that material from plants under development for food use is inadvertently present in the food supply at low levels prior to having been the subject of a completed food safety consultation with FDA. FDA anticipates that firms participating in this program will continue to interact with FDA using the agency's premarket consultation procedures, which considers all relevant safety and regulatory questions associated with food from the variety.

⁸⁰ FDA/CVM is responsible for reviewing under its new animal drug authorities the safety and effectiveness of an introduced rDNA construct in the genome of an animal, including animal health, human and animal food safety, and whether the desired trait is expressed. See *FDA Guidance for Industry 187*, available online at: <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf>.

⁸¹ Livestock includes horses, cattle, bison, sheep, goats, swine, cervids, poultry, and other farm-raised animals, including farm-raised fish.

Product Area	Source Organism or Culture		
	<i>Genetically Engineered Plant</i>	<i>Genetically Engineered Animal</i>	<i>Genetically Engineered Microbe or Cultured Cell</i>
Food for animals	<u>USDA/APHIS</u> If plant poses a plant pest risk <u>FDA/CVM</u> ⁸⁴ <u>EPA/OPP</u> If plant-incorporated protectant is produced by plant, EPA/OPP regulates the pesticide substance and related genetic material for human and environmental safety, including the safety of dietary exposures to pesticide residues in human and animal food.	<u>FDA/CVM</u> <u>USDA/APHIS</u> If animal poses a plant pest risk <u>USDA/APHIS/VS</u> If animal poses health risk to livestock ⁸¹	<u>FDA/CVM</u>
Drug for humans	<u>FDA/CDER</u> <u>USDA/APHIS</u> If plant poses a plant pest risk	<u>FDA/CVM</u> <u>FDA/CDER</u>	<u>FDA/CDER</u>

⁸² FDA/CFSAN has responsibility for ensuring that most food for human consumption (whether derived from genetically engineered sources or non-genetically engineered sources) is safe, sanitary and properly labeled. FDA shares this responsibility with USDA/FSIS.

⁸³ USDA/FSIS is responsible for ensuring that the nation's commercial supply of meat, poultry, egg products, and fish of the Order Siluriformes is safe, wholesome, and correctly labeled and packaged.

⁸⁴ FDA has a voluntary food safety and regulatory consultation process for human and/or animal foods derived from genetically engineered plant varieties to be used in the food supply and recommends that developers of such products partake in the consultation process early in the development process (see <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Biotechnology/ucm096095.htm>). Particular uses of foods (including food substances) may be subject to certain premarket requirements; the fact that a food or food substance does or does not come from a genetically engineered plant has no bearing on those requirements. FDA also conducts a program that is focused on the early food safety evaluation of new non-pesticidal proteins produced by new plant varieties under development for food use. The program is designed to pro-actively address food safety concerns that might result in the event that material from plants under development for food use is inadvertently present in the food supply at low levels prior to having been the subject of a completed food safety consultation with FDA. FDA anticipates that firms participating in this program will continue to interact with FDA using the agency's premarket consultation procedures which considers all relevant safety and regulatory questions associated with food from the variety.

Product Area	Source Organism or Culture		
	<i>Genetically Engineered Plant</i>	<i>Genetically Engineered Animal</i>	<i>Genetically Engineered Microbe or Cultured Cell</i>
Biological product for humans	<u>FDA/CBER</u> or <u>FDA/CDER</u> ⁸⁵ <u>USDA/APHIS</u> If plant poses a plant pest risk	<u>FDA/CVM</u> <u>FDA/CBER</u> or <u>FDA/CDER</u>	<u>FDA/CBER</u> or <u>FDA/CDER</u>
Medical device or medical diagnostic for humans	<u>FDA/CDRH</u> <u>USDA/APHIS</u> If plant poses a plant pest risk	<u>FDA/CVM</u> <u>FDA/CDRH</u>	<u>FDA/CBER</u> or <u>FDA/CDRH</u> ⁸⁶
Drug for animals	<u>FDA/CVM</u> <u>USDA/APHIS</u> If plant poses a plant pest risk	<u>FDA/CVM</u>	<u>FDA/CVM</u>
Biological product for animals (veterinary biologic) ⁸⁷	<u>USDA/APHIS</u> If plant poses a plant pest risk <u>USDA/APHIS/VS/CVB</u>	<u>FDA/CVM</u> If rDNA construct itself does not meet the veterinary biologic definition <u>USDA/APHIS/VS/CVB</u>	<u>USDA/APHIS/VS/CVB</u>

⁸⁵ FDA/CBER and FDA/CDER each have regulatory responsibility, including premarket review and oversight, for human biological products within their jurisdictions.

⁸⁶ FDA/CBER and FDA/CDRH each have regulatory responsibility for certain medical devices. While FDA/CDRH has regulatory responsibility for most medical devices, FDA/CBER generally has regulatory responsibility for medical devices related to licensed blood and cellular products. For additional information regarding the division between FDA/CDRH and FDA/CBER of regulatory responsibility for medical devices, please see *Intercenter Agreement Between the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health*, available online at: <http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121175.htm>.

⁸⁷ A veterinary biologic produced and distributed in full conformance with the Virus-Serum-Toxin Act, 21 U.S.C. §§ 151-159, and any implementing regulations is not subject to new animal drug review under the FD&C Act. See 21 C.F.R. § 510.4.

Product Area	Source Organism or Culture		
	<i>Genetically Engineered Plant</i>	<i>Genetically Engineered Animal</i>	<i>Genetically Engineered Microbe or Cultured Cell</i>
Medical device for animals	<u>FDA/CVM</u> <u>USDA/APHIS</u> If plant poses a plant pest risk	<u>FDA/CVM</u>	<u>FDA/CVM</u>
Cosmetics	<u>FDA/CFSAN</u> <u>USDA/APHIS</u> If plant poses a plant pest risk	<u>FDA/CVM</u> <u>FDA/CFSAN</u>	<u>FDA/CFSAN</u>
Industrial or consumer chemicals, including pesticide intermediates	<u>USDA/APHIS</u> If plant poses a plant pest risk	<u>FDA/CVM</u> ⁸⁸	<u>EPA/OPPT</u> If microbe is intergeneric, and is manufactured or processed for commercial production purposes, ⁸⁸ including research and development (R&D) for commercial purposes, ⁸⁹ for a use that is not excluded under TSCA, ⁹⁰ nor otherwise exempt from reporting ⁹¹

⁸⁸ New chemicals that are not specifically excluded are subject to EPA's oversight and TSCA premanufacturing review.

⁸⁹ Commercial R&D means that the activities are conducted with the purpose of obtaining an immediate or eventual commercial advantage and it includes R&D funded directly by a commercial entity regardless of who is actually conducting the research and R&D not funded directly by a commercial entity, if the researcher intends to obtain an immediate or eventual commercial advantage

⁹⁰ Exclusions from TSCA are food, food additives, drugs, cosmetics, medical devices, pesticides (but not pesticide intermediates), tobacco, nuclear material, and firearms. See TSCA Section 3(2)(B), 15 U.S.C. § 2602(2)(B).

⁹¹ A person who manufactures, imports, or processes a microorganism is not subject to reporting requirements if the microorganism is solely for research and development activities; the microorganism is used by, or directly under the supervision of, a technically qualified individual (TQI) as defined in § 725.3 and the TQI maintains documentation of the procedures selected to ensure compliance; there is no intentional testing of a microorganism outside of a building or vessel which effectively surrounds and encloses the microorganism and includes features designed to restrict the microorganism from leaving; and there are containment and/or inactivation controls. See 40 C.F.R. §§ 275.234-275.235.

Product Area	Source Organism or Culture		
	<i>Genetically Engineered Plant</i>	<i>Genetically Engineered Animal</i>	<i>Genetically Engineered Microbe or Cultured Cell</i>
Biomass conversion for chemical production, microbial fuel cells, mining and resource extraction, building materials, waste remediation and pollution control, non-pesticidal agriculture applications like biofertilizers, weather and climate modification, various consumer products, and all other applications of intergeneric microbes not otherwise excluded under TSCA ⁹²	Not applicable to this product area	Not applicable to this product area	<u>EPA/OPPT</u> If microbe is intergeneric, and is manufactured or processed for commercial production purposes, ⁸⁸ including R&D for commercial purposes, ⁸⁹ for a use that is not excluded under TSCA, ⁹⁰ and is not otherwise exempt from reporting. ⁹¹
Other (non-food, non-chemical producing, non-drug producing, non-biologic producing, non-pesticidal organisms) ⁹³	<u>USDA/APHIS</u> For ornamental, silvicultural, or turfgrass crops, if plant poses a plant pest risk <u>USDA/APHIS</u> For ornamental, silvicultural, or turfgrass crops, if plant poses plant noxious weed risk	<u>FDA/CVM</u> <u>USDA/APHIS</u> If animal poses a plant pest risk <u>USDA/APHIS/VS</u> If animal poses health risk to livestock ⁶⁵	<u>USDA/APHIS</u> If plant-associated microorganism poses a plant pest risk <u>EPA/OPPT</u> If microbe is intergeneric, and is manufactured or processed for commercial production purposes, ⁸⁸ including R&D for commercial purposes, ⁸⁹ for a use that is not excluded under TSCA, ⁹⁰ and is not otherwise exempt from reporting. ⁹¹

⁹² Exclusions from TSCA are food, food additives, drugs, cosmetics, medical devices, pesticides (but not pesticide intermediates), tobacco, nuclear material, and firearms. See TSCA Section 3(2)(B), 15 U.S.C. § 2602(2)(B).

⁹³ Pesticide intermediates are subject to TSCA, not FIFRA.

Product Area	Source Organism or Culture			
	<i>Genetically Engineered Plant</i>	<i>Genetically Engineered Animal</i>	<i>Genetically Engineered Microbe or Cultured Cell</i>	<i>Cell-free Synthesis or Isolates</i>
Pesticide ⁹⁴	<p><u>EPA/OPP</u> If plant-incorporated protectant is produced by plant, EPA/OPP regulates the pesticide substance and related genetic material for human and environmental safety, including the safety of dietary exposures to pesticide residues in human and animal food.</p> <p><u>USDA/APHIS</u> If plant poses a plant pest risk</p> <p><u>FDA/CFSAN</u> If human food, FDA/CFSAN oversees non-EPA-regulated aspects of the food for safety for human consumption.</p> <p><u>FDA/CVM</u> If animal food, FDA/CVM oversees non-EPA-regulated aspects of the food for safety for animal consumption.</p>	<p><u>EPA/OPP</u> If an animal is used as a pesticide, EPA/OPP ensures safety of human and animal food by regulating as chemical pesticide residues any animals or animal parts in the human or animal food, <i>e.g.</i>, predatory insects, predatory insect parts, or nematodes in grain.</p> <p><u>USDA/APHIS/BRS</u> If animal poses a plant pest risk</p> <p><u>FDA/CVM</u></p>	<p><u>EPA/OPP</u> If pesticide is a genetically engineered microbe, EPA/OPP regulates the microbial pesticide for human and environmental safety, including the safety of dietary exposure to pesticide residues in human and animal food. This also includes genetically engineered bacterial symbionts that are part of a nematode-bacterial entomopathogen complex.</p> <p><u>USDA/APHIS</u> If microbe poses a plant pest risk</p> <p><u>EPA/OPPT</u> Evaluates and potentially regulates a living genetically engineered microbe used as a pesticide intermediate, <i>i.e.</i>, where the “pesticide” product is the dead microbe</p> <p><u>FDA/CFSAN</u> If human food, FDA/CFSAN oversees non-EPA-regulated aspects of the food for safety for human consumption.</p> <p><u>FDA/CVM</u> If animal food, FDA/CVM oversees non-EPA-regulated aspects of the food for safety for animal consumption.</p>	<p><u>EPA/OPP</u> If nucleic acids produced via cell-free synthesis, or isolated from an organism are used for pesticidal purposes,⁹⁵ these products are regulated by EPA/OPP for human and environmental safety, including the safety of exposures to pesticide residues in human and animal food.</p>

⁹⁴ For certain antimicrobial uses, the antimicrobial is considered both a food additive and a pesticide under the Antimicrobial Regulation Technical Corrections Act of 1998 (ARCTA) with pesticide residue food safety regulated by FDA under the Federal Food, Drug, and Cosmetics Act (FD&C Act), and human and environmental safety regulated by EPA under FIFRA, *e.g.*, antimicrobials to preserve water contacting food where food processing occurs and food packaging preservatives.

⁹⁵ Examples of such pesticidal applications include double stranded RNA used for RNAi gene silencing.

E. Interagency Communication and Coordination

This section clarifies the mechanisms currently in place that enable communication and sharing of information, as appropriate and necessary, among EPA, FDA, and USDA. These mechanisms are particularly helpful with respect to regulation of products that fall under the purview of more than one agency or may necessitate close coordination prior to decision making.

1. Formal and Ad Hoc Interagency Working Groups

This Update to the Coordinated Framework and the accompanying *Strategy* were developed by the Biotechnology WG, which was established by the July 2015 EOP Memorandum under the ETIPC Committee. The Biotechnology WG will continue the work initiated to fulfill the goals identified in the July 2015 EOP Memorandum.

EPA, FDA, and USDA consult with each other and with other Federal agencies, as necessary, during their reviews of biotechnology products. For example, during the new animal drug review process, FDA may consult with other Federal agencies such as EPA, the U.S. Fish and Wildlife Service (FWS), National Marine Fisheries Service, and/or the U.S. Centers for Disease Control and Prevention (CDC). Similarly, other Federal agencies and departments, such as the National Institutes of Health, Department of Defense, Department of Homeland Security, Department of Commerce, Department of State, and others, are informed and consulted, as necessary and relevant. In addition, ad hoc working groups are formed, when appropriate, to facilitate discussions among relevant agencies. Another example of coordination among the Federal agencies occurs during the review of a new herbicide-resistant plant and registration of the herbicide that would be used on the plant. Such coordination is aimed at promoting use of the best available science for each agency's decision making, including assessment of best management practices for effective herbicide resistance management.

2. Memoranda of Understanding

EPA, FDA, and USDA have put in place memoranda of understanding (MOUs⁹⁶) to enhance coordination and enable sharing of information among the agencies. Below are descriptions of current MOUs specific to biotechnology products.^{97,98}

- In July 2009, the EPA's Office of Pesticide Programs' Biopesticide and Pollution Prevention Division and USDA's Animal and Plant Health Inspection Service's Biotechnology Regulatory Services (BRS) entered into a science review work share MOU (09-2000-0052-MU) for the purpose of sharing and utilizing science reviews of product characterization of PIPs. Both EPA and USDA review PIP product characterization data in support of their regulatory actions. This MOU established processes and procedures for reciprocal review of company-submitted product characterization data, sharing the resulting data evaluation records, and utilizing them for their own statute-specific scientific assessments. The MOU identifies the general principle of cooperation and communication the two agencies will utilize for such reviews to enhance the effectiveness and efficiency of the U.S. Government's regulation of PIPs.

⁹⁶ An MOU is a formal arrangement between an agency and other Federal, state, or local government agencies; academic institutions; and other entities. The MOU constitutes an understanding between the parties but is a non-binding arrangement.

⁹⁷ Other MOUs that are generally applicable to an agency's programs may also be relevant to the agency's regulation of biotechnology products. For example, in 2015, FDA's Foods and Veterinary Medicine Program (including CFSA and CVM) and EPA's Office of Chemical Safety and Pollution Prevention established a formal mechanism, through an MOU, to share information in areas of mutual interest, consistent with programmatic goals and resources that will assist in public health protection and the effective and efficient execution of Federal responsibilities. (See <http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm457193.htm>.) As another example, in 2012, FDA and USDA developed an MOU that establishes policies and procedures to enhance the exchange of information between participating agencies of USDA and FDA related to food safety, public health, and associated regulatory, marketing, trade, and research activities substantially affecting the public health (See <http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm294512.htm>.) Likewise, in February of 2013, FDA and USDA/APHIS re-established a Memorandum of Understanding to clarify procedures and responsibilities to resolve jurisdictional issues and questions concerning the regulation of certain animal products such as veterinary biologicals under the VSTA, or as drugs under the FD&C Act. The MOU establishes a standing committee comprised of experts from the Center for Veterinary Medicine (FDA) and the Center for Veterinary Biologics (APHIS), who review proposed products cooperatively to establish jurisdictional authority (See <http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm359217.htm>.) For more information about FDA's MOUs, see <http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/default.htm>.

⁹⁸ USDA also has internal MOUs that may be applicable to USDA programs such as one related to testing services in the event of a compliance incident involving a regulated product between USDA/APHIS and USDA's Agricultural Marketing Service and Grain Inspection, Packer and Stockyards Administration.

- On February 2, 2011 the EPA, FDA and USDA/APHIS Biotechnology Regulatory Services (BRS) entered into an MOU (10-2000-0058-MU; 225-11-0001) to support and encourage cooperation and communication among the three agencies in the regulatory oversight over genetically engineered plants and the foods derived from such plants.⁹⁹ Under this MOU, the three agencies agree to share information about GE plants and the foods derived from such plants, including non-public information exempt from public disclosure. The three agencies entered into this MOU to share, on a reciprocal and as-needed basis, non-public information related to the three agencies' respective programs regulating genetically engineered plants and the foods derived from such plants.
- On October 22, 2012, the EPA Office of Chemical Safety and Pollution Prevention (OCSPP) Office of Pesticide Programs (OPP), USDA/APHIS Plant Protection and Quarantine (PPQ), and USDA/APHIS Biotechnology Regulatory Services (BRS) entered into the *Microbial Pesticide Memorandum of Understanding*. Under this memorandum, EPA/OCSPP/OPP, USDA/APHIS/PPQ, and USDA/APHIS/BRS agree to share, on a reciprocal basis, information on microbial pesticides related to their respective programs regulating microorganisms.

Finally, as a general matter, when EPA, FDA, or USDA need expertise from other agencies to assess fully the safety of a biotechnology product, that expertise can be accessed through interagency communication. For example, the CDC, the FWS, National Marine Fisheries Service, National Invasive Species Council, and other agencies have been called upon, from time to time, to provide such expertise.

F. Future Reviews of and Updates to Coordinated Framework

This subsection describes the timeline and mechanism for the review of and, if necessary, update to, the Coordinated Framework. The July 2015 EOP Memorandum stated that for at least five years, starting one year after the release of the *Strategy*, the Biotechnology WG will produce an annual report on specific steps that agencies are taking to implement that *Strategy* and any other steps that the agencies are taking to improve the transparency, coordination, predictability, and efficiency of the regulation of biotechnology products. This report will be made available to the public by the EOP.

At the end of this work, the Biotechnology WG is expected to continue monitoring scientific and technical developments in biotechnology and its applications, and to work with stakeholders to undertake future updates to the Coordinated Framework as warranted.

⁹⁹ Available online at: <https://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2011-0038>.

G. Clarifying Roles and Responsibilities through Case Studies

Target Audience

This section 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. This section 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 as described earlier in this document. More information on such requirements is available in relevant agency regulations and guidance. The individual regulatory path that a product takes is based on its characteristics and application, as one or both can affect the regulatory status and relevant requirements established in the various regulations that underlie the Coordinated Framework.

Introduction

The primary Federal agencies that regulate biotechnology products are the U.S. Food and Drug Administration (FDA), the U.S. Environmental Protection Agency (EPA), and the U.S. Department of Agriculture (USDA). The Coordinated Framework, 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 Coordinated Framework is based on laws older than the Coordinated Framework 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 the publication of the Coordinated Framework has enabled the agencies to describe 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 below in the form of case studies. A number of the case studies are based on

general product classes that have completed the regulatory processes and may be in commercial use today. However, they do not necessarily represent developers' actual products.

The case studies presented in this document were selected because they cover multiple biotechnology product areas with different characteristics and applications, and because they illustrate how agencies coordinate their oversight under the Coordinated Framework. Other nuances exist; for example, exemptions for certain products within the regulatory system can affect the path forward. The case studies touch on these as appropriate. The case studies presented here cover typical relevant milestones, from the identification of a potentially commercially viable biotechnology product, to R&D activities in the laboratory and the field, to commercialization.

Recognizing that intricacies exist in any regulatory system, EPA, FDA, and USDA welcome and encourage developers of biotechnology products to contact the agencies at the early stages of product discovery or 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.

The scenarios below do not necessarily reflect the comprehensive requirements and/or policies of all relevant Federal agencies with respect to particular products and should not be construed as an official Federal opinion or decision on any particular matter.

Case Study #1: Hypothetical Genetically Engineered Corn with Pesticidal Properties

A hypothetical 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?

- EPA Regulates the pesticidal trait in the plant.
- FDA The corn will be used for food for humans and/or animals.
- USDA Regulates the corn plant engineered with plant pest components.

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 corn will be imported into the United States or transported across state lines, the developer must obtain an import or interstate shipment *authorization (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 corn does not fit an existing categorical exclusion under NEPA,¹⁰⁰ 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 corn into the test field.

As the corn is for food use, at this stage, the developer either (1) obtains 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 (FD&C Act); or (2) destroys any crops with residues of the pesticide.

Additionally, because the corn will be used for food for humans and/or animals and the developer must ensure that the corn and any derived products to be used for food for humans and/or animals are safe and meet all other applicable FDA requirements, 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 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 more of land. The developer must obtain an *experimental use permit (EUP)* from EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

Because the developer must ensure that the corn and any derived products to be used for food for humans and/or animals are safe and meet all other applicable FDA requirements, if the developer has not already done so, it 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 corn. Similarly, if the developer has not already done so, it must obtain a *tolerance* or *tolerance exemption* from EPA or ensure that all experimental crops with residues of the pesticide are destroyed.

¹⁰⁰ When a genetically engineered organism or product involves new species or organisms or novel modifications that potentially raise new issues, the

authorization may not qualify for a categorical exclusion.

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 corn.

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 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 must ensure that the corn and any derived products to be used for food for humans and/or animals are safe and meet all other applicable FDA requirements. The developer is strongly encouraged to complete a voluntary consultation with FDA about food from the corn to help ensure that any food safety or other FDA-related regulatory issues are resolved prior to marketing.

VII. Public engagement

EPA: EPA, under its FIFRA and FD&C Act authorities, offers the public opportunities to comment at several points during significant regulatory actions. These include public notices at the receipt of an application, prior to preliminary decisions, and prior to final decisions.

FDA: FDA posts the results of the completed consultation on its website.

USDA: The first public comment opportunity occurs shortly after receipt of a petition for nonregulated status to provide input for APHIS to consider as it develops the EA or EIS and the Plant Pest Risk Assessment (PPRA). The second opportunity for public engagement occurs after development of an EA or EIS and the PPRA. The second opportunity may include public meetings. APHIS may also decide, based on the public's input and other factors, that an EIS is necessary, in which case APHIS will complete the NEPA EIS process in accordance with CEQ procedures. The public may have as many as three additional opportunities to provide input into the

decision making process if an EIS is prepared. APHIS may also conduct public meetings (in person or virtually) to accept oral and written comment on its analyses.

Case Study #2: A Hypothetical Genetically Engineered Plum with Pesticidal Properties

A hypothetical 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 Regulates the pesticidal trait in the plant.

FDA The 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 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 plum into the food supply for humans and/or animals, the developer either (1) obtains a *tolerance* or *tolerance exemption* for the residues of the pesticidal trait in the food from EPA under the FD&C Act; or (2) destroys any crops with residues of the pesticide.

Additionally, because the developer must ensure that the plum and any derived products to be used for food for humans and/or animals are safe and meet all other applicable FDA requirements, 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 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 more of land. The developer must obtain an EUP from EPA under FIFRA but does not need to obtain any authorizations from USDA/APHIS.

Because the plum will be used for food for humans and/or animals and the developer must ensure that the plum and any derived products to be used for food for humans and/or animals are safe and meet all other applicable FDA requirements, if the developer has not already done so, it 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 plum tree. Similarly, if the developer has not already done so, it must obtain a *tolerance* or *tolerance exemption* from EPA or ensure that all experimental crops with residues of the pesticide are destroyed.

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 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 must ensure that the plum and any derived products to be used for food for humans and/or animals are safe and meet all other applicable FDA requirements. The developer is strongly encouraged to complete a voluntary consultation with FDA about food from the plum tree to help ensure that any food safety or other FDA-related regulatory issues are resolved prior to marketing.

VII. Public engagement

EPA: EPA, under its FIFRA and FD&C Act authorities, offers the public opportunities to comment at several points during significant regulatory actions. These include public notices at the receipt of an application, prior to preliminary decisions, and prior to final decisions.

FDA: FDA posts the results of the completed consultation on its website.

Case Study #3: A Hypothetical Genetically Engineered Herbicide-resistant Canola

A hypothetical 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 *use* of the herbicide itself (including any new use of the herbicide), not the substance endowing the plant with tolerance to the herbicide or the genetic material necessary for production of the substance in the plant.
- FDA The 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 canola will be imported into the United States or transported across state lines, the developer must obtain an import or interstate shipment *authorization (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 trials¹⁰¹ are typically categorically excluded from NEPA. They still have regulatory requirements under the PPA, including keeping field trials confined. But because this canola fits an existing categorical exclusion under NEPA, USDA/APHIS will not prepare either an EA or EIS.

Because the developer ultimately intends to introduce the canola treated with the herbicide into the food supply for humans and/or animals, the developer either (1) obtains a *tolerance* or *tolerance exemption* for Herbicide X from EPA under the FD&C Act; or (2) destroys any crops with residues of the pesticide. Additionally, because the developer must ensure that the canola and any derived products to be used for food for humans and/or animals are safe and meet all other applicable FDA requirements, 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 canola. As part of these activities the developer may participate in FDA’s program focused on the early food safety evaluation of new non-pesticidal proteins produced by new plant varieties under development for food use. This program is designed to pro-actively address food safety concerns that might result in the event that material from plants under development for food use is inadvertently present in the food supply at low levels prior to having been the subject of a completed food safety consultation with FDA.¹⁰²

¹⁰¹ 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.

¹⁰² FDA anticipates that firms participating in this program will continue to interact with FDA using the agency’s premarket consultation procedures, which considers all relevant safety and regulatory questions associated with food from the variety.

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 more of land. The developer must amend the EPA registration of Herbicide X to allow for its use on canola (if inconsistent with the current label), obtain a new registration, or obtain from EPA an EUP for testing of Herbicide X on canola.

Because the developer must ensure that the canola and any derived products to be used for food for humans and/or animals are safe and meet all other applicable FDA requirements, if the developer has not already done so, it 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 canola. Similarly, if the developer has not already done so, it must obtain a *tolerance* or *tolerance exemption* from EPA or ensure that all experimental crops with residues of the pesticide are destroyed.

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

If the developer has not already done so, it must amend the EPA registration of Herbicide X to allow its use on canola or obtain a new registration and obtain from EPA a *tolerance* or *tolerance exemption* for the Herbicide X.

The developer must ensure that the canola and any derived products to be used for food for animals (or humans) are safe and meet all other applicable FDA requirements. The developer is strongly encouraged to complete a voluntary consultation with FDA about

food from the canola to help ensure that any food safety or other FDA-related regulatory issues are resolved prior to marketing.

VII. Public engagement

FDA: FDA posts the results of the completed consultation on its website.

USDA: The first public comment opportunity occurs shortly after receipt of a petition for nonregulated status to provide input for APHIS to consider as it develops the EA or EIS and the PPRA. The second opportunity for public engagement occurs after development of an EA or EIS and the PPRA. The second opportunity may include public meetings. APHIS may also decide, based on the public's input and other factors, that an EIS is necessary, in which case APHIS will complete the NEPA EIS process in accordance with CEQ procedures. The public may have as many as three additional opportunities to provide input into the decision making process if an EIS is prepared. APHIS may also conduct public meetings (in person or virtually) to accept oral and written comment on its analyses.

Case Study #4: A Hypothetical Genetically Engineered Rose

A hypothetical 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 genetically engineered with plant pest components, and is for ornamental use only.¹⁰³

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

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

If the rose does not fit an existing categorical exclusion under NEPA,¹⁰⁴ 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 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 rose. In most cases, nonregulated status is granted prior to commercialization. However, it is not a prerequisite and commercialization may proceed under permit.

VII. Public engagement

USDA: The first public comment opportunity occurs shortly after receipt of a petition for nonregulated status to provide input for APHIS to consider as it develops the EA or EIS and the PPRA. The second opportunity for public engagement occurs after development of an EA or EIS and the PPRA. The second opportunity may include public meetings. APHIS may also decide, based on the public's input and other factors, that an EIS is necessary, in which case APHIS will complete the NEPA EIS process in accordance with CEQ procedures. The public may have as many as three additional opportunities to provide input into the decision making process if an EIS is prepared. APHIS may also conduct public meetings (in person or virtually) to accept oral and written comment on its analyses.

¹⁰³ In such cases, it is the responsibility of those marketing the rose in the U.S. to ensure that the rose does not enter the food supply.

¹⁰⁴ When a genetically engineered organism or product 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: A Hypothetical Genetically Engineered Microbial Pesticide—Not a Plant Pest

A hypothetical 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 comprises the genetically engineered 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 genetically engineered 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 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 microbial pesticide will be released into the environment for a field test (cumulative plot size at or less than 10 acres of land), the developer must submit a *biotechnology notification*¹⁰⁵ to EPA to determine whether or not an EUP is required under FIFRA. If the

field trial cumulative plot size is 10 acres or more see section V.

Because the developer intends to introduce crops treated with the microbial pesticide into the food supply for humans and/or animals, the developer either (1) obtains a *tolerance* or *tolerance exemption* for the genetically engineered microbial pesticide from EPA under the FD&C Act; or (2) destroys any crops with residues of the pesticide.

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 more of land. The developer must obtain an EUP from EPA under FIFRA and, if it has not already done so, a *tolerance* or *tolerance exemption* under the FD&C Act or ensure that all experimental crops with residues of the pesticide are destroyed.

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 microbial pesticide.

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

VII. Public engagement

EPA: EPA, under its FIFRA and FD&C authorities, offers the public opportunities to comment at several points during significant regulatory actions. These include public notices at the receipt of an application, prior to preliminary decisions, and prior to final decisions.

¹⁰⁵ *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 C.F.R. § 172.45).

Case Study #6: A Hypothetical Genetically Engineered Microbial Pesticide—A Plant Pest

A hypothetical 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 genetically engineered *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 genetically engineered 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).

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

If the microbial pesticide that is a plant pest will be imported into the United States, the developer must obtain from USDA/APHIS an import *permit* (authorizations for plant pest do not qualify for the

notification procedures) and from EPA a *pesticide notice of arrival*.

If the 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 (permit) for environmental release* from USDA/APHIS.

If the microbial pesticide does not fit an existing categorical exclusion under NEPA,¹⁰⁶ 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*¹⁰⁷ to EPA to determine whether or not an EUP will be required under FIFRA.

Because the developer intends to introduce crops treated with the microbial pesticide into the food supply for humans and/or animals, the developer either (1) obtains a *tolerance* or *tolerance exemption* for the genetically engineered microbial pesticide from EPA under the FD&C Act; or (2) destroys any crops with residues of the pesticide.

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

In addition to its responsibilities triggered by small-scale field trials, the developer must obtain an EUP from EPA under FIFRA if the field trial cumulative plot size is 10 acres or more of land.

If the developer has not already done so, it must obtain a *tolerance* or *tolerance exemption* from EPA or ensure that all experimental crops with residues of the pesticide are destroyed.

VI. What must a developer do prior to commercialization?

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 C.F.R. § 172.45).

¹⁰⁶ When a genetically engineered organism or product involves new species or organisms or novel modifications that potentially raise new issues, the authorization may not qualify for a categorical exclusion.

¹⁰⁷ *Biotechnology notifications* are required prior to experimental activities on small test plots to allow

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

The developer must receive a *permit* for importation or interstate movement, a *pesticide notice of arrival* when imported, and a *permit 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 inoculated 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 (permit)*.

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

VII. Public engagement

EPA: EPA, under its FIFRA and FD&C authorities, offers the public opportunities to comment at several points during significant regulatory actions. These include public notices at the receipt of an application, prior to preliminary decisions, and prior to final decisions.

USDA: The first public comment opportunity occurs shortly after receipt of a petition for nonregulated status to provide input for APHIS to consider as it develops the EA or EIS and the PPRA. The second opportunity for public engagement occurs after development of an EA or EIS and the PPRA. The second opportunity may include public meetings. APHIS may also decide, based on the public's input and other factors, that an EIS is necessary, in which case APHIS will complete the NEPA EIS process in accordance with CEQ procedures. The public may have as many as three additional opportunities to provide input into the decision making process if an EIS is prepared. APHIS may also conduct public meetings (in person or virtually) to accept oral and written comment on its analyses.

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 α S(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.

Case Study #8: 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 with the extracted algal biomass used for fish food. (Note that this case illustrates the separation of products subject to TSCA from those subject to FD&CA)

I. The product

The eukaryotic microalga *Chlamydomonas reinhardtii* is genetically engineered to produce more effective lipid biosynthesis. The newly produced and extracted triacylglycerols (TAGs) will be later converted into specific products that may include biodiesel, jet fuel or lubricants. The genetic sequences that increase lipid production were identified through metagenomic analysis and apparently come from an unidentified chlorophyte alga not related to *Chlamydomonas*. They are synthetically codon optimized to work best in *Chlamydomonas*. The key introduced gene is controlled by the cauliflower mosaic virus-derived 35S promoter (CaMV). A plasmid encoding the new enzyme sequences, the promoter, and a selection marker is introduced into the alga through electroporation. *C. reinhardtii* will be cultivated in an open pond system. The extracted microalgae biomass from the TAG production processes will be sent to other customers for processing as animal food.

II. Which agencies have oversight and why?

USDA The microalga is engineered with a plant pest component (CaMV 35S promoter).

EPA The microalga is engineered for industrial use with genes from outside the genus *Chlamydomonas* (both due to a likely source from another genus and because they are synthetic sequences) is not currently on the TSCA Chemical Substance Inventory and as such is considered “new” and falls under

rules implementing the Toxic Substances Control Act (TSCA).¹⁰⁸

FDA The algal biomass resulting from additional processing of the extracted microalgae will be used as food for 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). EPA’s TSCA regulations provide conditions to ensure certain R&D is contained. Under TSCA, EPA regulations exempt reporting, provided certain conditions are met.¹⁰⁹

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,¹¹⁰ 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.

The organism is used to manufacture a product not subject to FDA oversight (a non-food co-product) and is thus subject to TSCA oversight. 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.¹¹¹

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

¹⁰⁸ EPA is required under TSCA section 8(b), 15 U.S.C. 2607(b), to compile and keep current a list of chemical substances manufactured (including imported) or processed in the United States. This list is known as the TSCA Chemical Substance Inventory or simply the “TSCA Inventory.” A chemical substance not on TSCA Inventory is considered a “new chemical substance.” See TSCA section 3(11), 15 U.S.C. 2602(11).

¹⁰⁹ 40 C.F.R. 725.205 - 235

¹¹⁰ 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.

¹¹¹ If risk-associated issues are identified during the TERA review, EPA may extend period of review beyond 60 days.

additional processing of the extracted microalgae biomass.

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

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 an 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 from the required agencies. 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 and commercialization may proceed under permit. To avoid these requirements, a developer may petition USDA/APHIS for nonregulated status.

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. EPA must make an affirmative determination on the MCAN. If EPA determines that the product is not likely to present an unreasonable risk of injury to health or the environment, the developer is free to initiate commercial activity. If EPA determines that the product presents an unreasonable risk or that available information is insufficient to permit a reasoned

evaluation of the health and environmental effects of the product, EPA must issue an order to address the risks or potential risks. EPA typically would work to negotiate a consent order. Upon receipt of a Notice of Commencement of Manufacture, the microorganism would be placed on the TSCA Inventory of Chemical Substances (Inventory) and would no longer be considered new. EPA would also issue a Significant New Use Rule if warranted.

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 must ensure that the animal food derived from additional processing of the extracted microalgae biomass is safe for its intended use and meets all other applicable requirements. The developer is strongly encouraged to consult with FDA about animal food uses of the residual biomass from the non-food production processes to help ensure that any food safety or other FDA-related regulatory issues¹¹² are resolved prior to marketing.

¹¹² As an example, food safety or other regulatory issues could involve the presence of an unapproved food additive in the resulting animal food product.

Appendix 1: Fall 2015 RFI and Public Comments

On October 6, 2015, the NSTC published a notice of request for information (RFI) in the Federal Register¹¹³ to solicit relevant data and information, including case studies, that could assist in the development of the proposed Update to the Coordinated Framework and the development of the long-term strategy consistent with the objectives described in the July 2015 EOP Memorandum. Approximately 900 responses had been submitted to the public docket when the comment period closed on November 13, 2015 (accessible at www.regulations.gov).¹¹⁴

In addition, three public meetings in three different regions of the country were held by OSTP, EPA, FDA, and USDA, under the auspices of the NSTC. The first public meeting was held on October 30, 2015, at the FDA's White Oak Campus in Silver Spring, Maryland, to inform the public about the activities described in the July 2015 EOP Memorandum, invite verbal comments from interested parties, and provide information about where and how to submit written comments, data, or other information.¹¹⁵ Verbal comments made by individual members of the public at this meeting were submitted to the docket as part of the official meeting transcript.¹¹⁶

The second public meeting was held on March 9, 2016 at EPA's Region 6 Office in Dallas, Texas.¹¹⁷ The primary purpose of that meeting was to illustrate current Federal roles and responsibilities regarding biotechnology products. Representatives from OSTP, EPA, FDA, and USDA reviewed progress made on the tasks identified in the July 2015 EOP Memorandum and illustrated the current regulatory roles and responsibilities through a discussion of product case studies. Verbal comments made by individual members of the public at this meeting were submitted to the docket as part of the official meeting transcript.¹¹⁸

¹¹³ Clarifying Current Roles and Responsibilities Described in the Coordinated Framework for the Regulation of Biotechnology and Developing a Long-Term Strategy for the Regulation of the Products of Biotechnology, 80 FR 60414 (Oct. 6, 2015). Available online at: <https://www.federalregister.gov/articles/2015/10/06/2015-25325/clarifying-current-roles-and-responsibilities-described-in-the-coordinated-framework-for-the>.

¹¹⁴ See <http://www.regulations.gov/#!docketDetail;D=FDA-2015-N-3403>.

¹¹⁵ Modernizing the Regulatory System for Biotechnology Products: First Public Meeting, 80 FR 62538. Available online at: <http://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm463783.htm>.

¹¹⁶ See <http://www.regulations.gov/docket?D=FDA-2015-N-3403>.

¹¹⁷ Modernizing the Regulatory System for Biotechnology Products: Three Public Meetings. Available online at: <https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/modernizing-regulatory-system-biotechnology-products>.

¹¹⁸ See <http://www.regulations.gov/docket?D=FDA-2015-N-3403>.

The third public meeting was held on March 30, 2016, at the University of California's Davis Conference Center in Davis, California.¹¹⁹ Similar to the second public meeting, representatives from each of the three primary regulatory agencies and OSTP reviewed progress made and illustrated the current regulatory roles and responsibilities of the agencies related to biotechnology products through a discussion of hypothetical product case studies. The meeting also included breakout listening sessions focusing on three general thematic areas relevant to the tasks identified in the July 2015 EOP Memorandum: (1) Governance; (2) Education, Communication, and Outreach; and (3) Improving Regulatory Certainty. The goal of each breakout listening session was to provide individual participants the opportunity to share their thoughts and perspectives on the regulation of biotechnology products in the U.S. To provide context for the participants, the agencies provided a set of questions to be considered under each thematic area. Individuals attending the meeting selected the breakout session in which they wished to participate. Notes were taken during the discussion by agency representatives in each session and summaries placed in the docket established by the agencies for the Coordinated Framework updating effort.¹²⁰ Verbal comments offered by individual members of the public made at the close of the meeting have also been placed in the docket as part of the official meeting transcript.

A. Summary of Public Responses to RFI and Public Meeting Input

OSTP, EPA, FDA, and USDA reviewed and considered all public responses received, including comments in response to the RFI and comments received during the three public meetings, during the development of the proposed Update to the Coordinated Framework and the associated *Strategy*. The written and verbal comments were submitted by U.S. and international industry, academia, trade associations, consumer groups, environmental groups, individual consumers, and other organizations. Below is a brief summary of issues raised in the responses.

1. General Responses

Several responses favored the use of risk-based, science-based regulatory systems and a coordinated framework that facilitates (or does not stifle) innovation, reduces burden to industry, particularly to small and mid-sized businesses and public-sector researchers, and does not discourage innovative “start-ups” from entering the field. Some responses requested balance between the level of regulation and the degree of risk posed by a new trait or an existing trait in a new environment, while others noted that the complexities of the current regulatory system have made it difficult for small and mid-sized companies, public-sector researchers, and academics to navigate the system. Some responses sought uniform regulation across products rather than regulation based on the process of production. Other responses discussed expanding exemptions and fast-tracking product reviews. In contrast, some others recommended regulating based on process, using genetic engineering, in and of itself, as the trigger for mandatory premarket review of products. Some responses recommended that agencies harmonize their regulatory

¹¹⁹ Modernizing the Regulatory System for Biotechnology Products. Available online at: https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/stakeholder-meetings/cf_meeting.

¹²⁰ <http://www.regulations.gov/docket?D=FDA-2015-N-3403>.

approaches with Codex guidelines and coordinate with international regulatory trading partners on the regulation of emerging technologies to promote approaches that do not unnecessarily hinder trade and competitiveness in biotechnology products.

2. Responses Related to Public Education, Awareness, and Outreach

Several responses supported agencies taking action regarding public education, awareness, and training on genetic engineering, generally, as well as on specific applications of this technology. Some responses noted the need for simple and easy-to-understand information about how agencies regulate products and coordinate their respective roles/responsibilities. In this context, some responses also recommended providing this information on a single U.S. Government website or through another centralized resource. Some responses also stated that scientific evidence and information underlying regulatory decisions should be made easily available and accessible to the public. One response suggested that each agency should develop safety and security training programs for researchers and hobbyists.

3. Responses Related to Coordination among Regulatory Agencies

Several responses expressed the need for better coordination among regulatory agencies, including on risk assessments and data collection on unintended consequences. One response suggested the creation of a “review” board consisting of representatives from all three regulatory agencies to review all new genetically engineered and non-genetically engineered crops. Another response suggested establishing a group of experts under the National Academy of Sciences (with representation from each regulatory agency) to determine whether a product is exempt from review and creating and publishing decision trees for developers to determine whether and which products are exempt. Several responses noted the need to streamline regulatory processes and procedures to expedite reviews or approvals. For example, one response suggested that, for site-specific insertions of genes, agencies could develop genome maps for each crop species noting where insertions do not have pleiotropic effects, so that the approval process for products that use those locations can be expedited. Another response requested coordination among relevant agencies such that burden on industry with respect to obtaining multiple permits for conducting trials could be reduced. Some responses also identified specific case studies to highlight these concerns.

4. Responses Related to Governance

A number of individual commenters identified major points related to governance, *i.e.*, the need: (1) to broaden the concept of governance to include a wider community, such as farmers and affected industry groups, and (2) to identify stewardship functions of non-governmental participants.

5. Responses Related to Current Regulatory Approach and Improving Regulatory Certainty

Several responses addressed the current approach to regulation of biotechnology products. While some responses urged less regulation and/or noted that the current regulatory system is adequate to ensure safety of biotechnology products, others asked agencies to take additional actions to ensure the safety of biotechnology products. For example, with respect to foods

derived from GE sources, several commenters, citing safety and/or economic concerns with biotechnology products, recommended banning the marketing of all foods and food ingredients derived from GE sources. Other recommendations included that FDA require mandatory premarket evaluations, conduct or rely on independent safety studies (including long-term and/or multi-generational animal feeding studies), use third-party reviews of safety data, and require mandatory environmental assessments for all foods derived from GE sources. More broadly, commenters recommended that agencies implement postmarket surveillance programs to ensure the traceability of GE ingredients or components of biotechnology products.

Responses also expressed interest in greater certainty in regulatory processes. For example, commenters asked agencies to clarify their roles in the regulation of products with more than one use; regulatory oversight of field trials; regulation of GE insects; and regulation of genome-edited organisms used for various purposes.

Other specific recommendations for agencies to consider included:

- Identifying and establishing appropriate restrictions related to GE plants. Recommendations for such restrictions included a moratorium on specific traits, limitations on specific purposes (*e.g.*, restrictions on “herbicide-tolerant” or “pesticide-tolerant” crops), restrictions on where and how GE crops are grown so as to minimize potential for cross-contamination; and/or restrictions on privately-owned GE seed stock;
- Adopting a U.S. Federal regulatory policy for low level presence of GE sources in food for humans and animals, and seeds;
- Redefining “biotechnology product” to mean “strictly the living organism produced via addition, deletion, or modification of genetic material” or clarifying that “genetic engineering” also encompasses genome editing;
- Increasing resources and funding for risk assessments to support the identification of regulatory exemptions; for example, reserving five percent of Federal synthetic biology funding for risk assessment;
- Exempting DNA from the TSCA review process;
- Assessing the risk that products could evolve beyond their designed capacity; and
- Implementing mechanisms to perform long term studies on use of biotechnology-derived products.

B. Biotechnology WG Review of Public Responses

The Biotechnology WG (and relevant experts within OSTP, EPA, FDA, and USDA) reviewed all responses received. Some of the responses raised issues that are within the scope of activities contemplated in the current update to the Coordinated Framework, which, per the July 2015 EOP Memorandum, is focused on clarifying the current roles and responsibilities of the agencies that regulate biotechnology products. The proposed Update to the Coordinated Framework provided an overview of EPA, FDA, and USDA’s statutory provisions, regulatory frameworks, and specific regulatory processes and procedures, which vary based on the product category, that are applicable to biotechnology products. The discussion also included the legal bases and rationale for those regulatory approaches. In addition, the document clarified jurisdiction over biotechnology products, including where a product or its source organism falls under the

jurisdiction of more than one agency. The Biotechnology WG expects the information in the proposed Update to the Coordinated Framework largely addresses those public responses that asked for clarification on current regulation of biotechnology products. Some responses raised issues that are more appropriately addressed under the *Strategy*, and those will continue to be considered as part of future work related to the implementation of that *Strategy*. In addition, as work continues in response to the July 2015 EOP Memorandum, additional actions will be considered to clarify regulatory processes and procedures.

Another set of public responses raised issues that are outside of the scope of the July 2015 Memorandum (*e.g.*, issues related to the regulation of nanotechnology; promotion of local farming of crops and animals; mandatory labeling of foods containing GE ingredients, compensation for GE crop contamination prevention measures taken by organic farmers). Comments outside of the scope were not considered in developing the proposed Update to the Coordinated Framework or in the development of the *Strategy*.

Appendix 2: Comments on 2016 Proposed Update to Coordinated Framework

On September 22, 2016, the NSTC published a notice of request for public comment in the Federal Register¹²¹ to solicit relevant comments that can assist in the finalization of the proposed Update to the Coordinated Framework to clarify the current roles and responsibilities of the EPA, FDA, and USDA consistent with the objectives described in the July 2015 EOP Memorandum. Approximately 46 responses had been submitted to the public docket when the comment period closed on November 1, 2016 (accessible at www.regulations.gov).¹²²

Summary of Public Comments

The EOP, EPA, FDA, and USDA reviewed and considered all public responses received in response to the September 22, 2016 notice of request for public comment during the development of this final Update to the Coordinated Framework. Below is a brief summary of issues raised in the responses. These comments are separated into three categories: general comments, specific comments, and other comments. The general comments provide general overviews of commenters' views of the Coordinated Framework and the efforts to modernize the regulatory system for biotechnology products. The specific comments provide more detail regarding what additional information the Biotechnology WG might provide to stakeholders regarding the transparency, coordination, predictability, and efficiency of the regulation of biotechnology products. Some of these comments were addressed with edits incorporated into this Final Update to the Coordinated Framework. Note also the Update to the Coordinated Framework provides an overview of EPA, FDA, and USDA's statutory provisions, regulatory frameworks, and specific regulatory processes and procedures, which vary based on the product category, that are applicable to biotechnology products. This discussion includes the legal bases and rationale for those regulatory approaches. In addition, the document clarifies jurisdiction over biotechnology products, including where a product or its source organism falls under the jurisdiction of more than one agency. The Biotechnology WG expects the information in the Update to the Coordinated Framework largely addresses those public comments that asked for clarification on current regulation of biotechnology products. Still other comments will be considered by the Biotechnology WG as part of future activities, including during the implementation of the *Strategy*. Finally, another set of comments raised issues that are outside of the scope of the July 2015 Memorandum. These comments were not considered.

I. General Comments

¹²¹ Clarifying Current Roles and Responsibilities Described in the Coordinated Framework for the Regulation of Biotechnology, 81 FR 65414 (September 22, 2016). Available online at: <https://www.regulations.gov/contentStreamer?documentId=FDA-2015-N-3403-0916&disposition=attachment&contentType=pdf>

¹²² See <http://www.regulations.gov/#!docketDetail;D=FDA-2015-N-3403>.

A. Generally supportive

Several commenters expressed support for the overarching principles for regulation that are articulated in the proposed Update to the Coordinated Framework, urging agencies to maintain a risk-based scientifically sound approach to biotechnology products, including those enabled by newer techniques.

One commenter noted the proposed Update to the Coordinated Framework is an excellent reference document that clearly explains the authorities and protection goals of each agency; periodic updates, particularly in light of the forthcoming National Academy of Sciences (NAS) study, will make this an even more useful reference for stakeholders.

Another commenter, although supportive of the science-based regulatory system, argued that the current effort to update the Coordinated Framework does not address the “serious issues related to the marketability and current lack of international regulatory coherence regarding the premarket regulatory review” of biotechnology crops. In this regard, the commenter recommended that agencies identify any gaps in the current U.S. approach and potential ways to address such gaps, including any new necessary statutory authorities.

Similarly, another commenter who supported the U.S. regulatory approach asserted that “the CF embraces a process-based regulatory regiment because it seeks to regulate based upon the rDNA process” and such “process-based trigger for mandatory regulation” is inconsistent with U.S. regulatory approach.

B. Generally opposed

In contrast, several other commenters generally opposed the principles and approach for regulation described in the Proposed Update to the Coordinated Framework, and recommended a substantial overhaul of the current regulatory system.

These commenters made several arguments, including that:

- the Coordinated Framework either has failed or is flawed in that regulation of biotechnology products is not based on the processes that create them and, therefore, it cannot address hazards that are novel and unique to genetic engineering;
- current laws are severely outdated and inadequate to consider distinctive risks posed by biotechnology and, therefore, FDA, USDA, and EPA do not have the proper statutory authority to regulate biotechnology products; (however, one commenter suggested that agencies, nevertheless, could use the existing laws more effectively to employ a process-based approach);
- an adequate system would be process-based (applying a precautionary principle, using GE as the trigger for regulation), requiring mandatory pre-market decisions for all biotechnology products (including those from newer techniques), incorporating rigorous human health and environmental safety assessments and independent long-term scientific review/testing, requiring mandatory labeling of products, and considering system-wide impacts (including environmental and economic impacts);
- the Proposed Update to the Coordinated Framework does not include actual updates or changes to the framework, but instead provides clarifications only;

- instead of relying on the existing patchwork of statutory authorities, a sufficient framework should include a forward-thinking gap analysis and assessment of current legal authorities, and should codify the process by which regulations are normalized across agencies and the temporal limitations of guidelines;
- if the federal government wants to increase public confidence in biotechnology products, agencies should use the opportunity in the July 2015 EOP memo to identify “changes to authorities, regulations, and policies, if needed” and seek necessary legal authorities from Congress for premarket approval and mandatory labeling of products; and
- Until new regulations are established to ensure the safety of GE products, all of the approvals, commercializations, and releases of any new genetically engineered organisms must be halted.

In addition, calling on agencies to adopt a new coordinated framework, one commenter asserted agencies must comply with NEPA and APA when enacting and implementing the new process.

II. Specific Comments

A. Comments Addressed in Final Update to the Coordinated Framework

The agencies edited the Update to the Coordinated Framework to address the comments listed below:

Agencies other than EPA, FDA, USDA

Some commenters pointed out the role of agencies other than EPA, FDA, and USDA in ensuring safety of biotechnology products. Two commenters recommended adding the U.S. Fish and Wildlife Service within the Coordinated Framework as an agency tasked with environmental assessments, particularly when an agency does not have necessary expertise. Yet another commenter referred to national security concerns to emphasize the need for involvement of the DOD, DHS, the Intelligence Community, the Department of Commerce, and the Department of State in the regulation and assessment of new innovations and applications of biotechnology.

Case-Studies

Specifically about case study 7, one commenter noted that there is no mention of environmental assessment to deal with the potential problem that might arise if the GE rabbits accidentally were released into the wild. The commenter recommended an environmental risk assessment should accompany reviews of GE organisms.

Lead Agency

Referring to the 1986 Coordinated Framework, which identified a “lead agency” for products requiring regulatory oversight and/or review from multiple agencies, one commenter pointed out that the Proposed Update to the Coordinated Framework does not mention “lead agencies” and noted that identification of a lead agency would make it clear to a potential applicant which agency to approach for an initial consultation. Another commenter asked for APHIS to be clearly identified as having the lead role and primary responsibility for regulatory assessments.

Post-market requirements, authorities

Two commenters recommended adding, within Section D of the Proposed Update to the Coordinated Framework, information about each agency's roles and responsibilities after a product has reached the marketplace, such as adverse event reporting requirements under FIFRA and authorities for FDA to remove adulterated products from the marketplace. These commenters believe sharing such information will help to promote public confidence in the comprehensive nature of the regulatory system.

Products not within the scope of regulation

Commenters asserted the document should clearly communicate that all biotechnology products are subject to regulatory oversight, regardless of whether they are subject to pre-market approval. Some of these commenters noted that for biotechnology products that are *not* within the scope of agency pre-market approval, agencies should better explain the underlying risk-based decision and assure the public that agencies continue to have authority to remove that product from the marketplace, if warranted. In this context, one commenter also noted that routine agency terminology (such as “not a regulated article”) is often mis-interpreted in the media. Another commenter asked what specific aspect of a GE plant, once self-determined not to have used a plant pest in any development step and that a noxious weed risk is not plausible, warrants an “Am I Regulated” letter of inquiry.

Specific edits

- One commenter noted, in Table 2 in Section D, the role of FDA-CVM in regulating animal feed could be better defined. The commenter also stated that lack of clarity about FDA's Center for Veterinary Medicine's (CVM) role in regulating animal feed has created regulatory uncertainty and delays for some firms.
- In Table 2 in Section D, the word “substance” should be substituted for the word “trait” when describing a plant-incorporated protectant.
- One commenter asked agencies to consider including more examples, such as a GE microbe/yeast, or its enzymes, used in a fermentation process to produce renewable chemicals or bio-based products that may be subject to both EPA and FDA oversight. The commenter suggested, as an example, an industrial biotechnology product such as genetically engineered yeast or enzymes used in fermentation, resulting in production of fuel (TSCA oversight) and potable alcohol and distiller's grains (FDA oversight). The commenter further stated the role of CVM for animal feed could be better described. The commenter suggested agencies to also consider adding a case study of a hypothetical GE microorganism producing food for humans or animals (which would involve both FD&C and TSCA reviews).
- With respect to Figure 3, FDA Regulation Relevant to Biotechnology Products (page 19): Under “Food for Humans” and “Food for Animals”, one commenter recommended including information about FDA's premarket process for new protein consultations. This commenter further stated “New Protein Consultations are an important component of the coordinated federal regulatory approach to inadvertent, intermittent, low-level presence of proteins in the food supply.”

- One commenter noted the following errors regarding Case Study #2: (1) “a public comment period related to an APHIS petition is described. As the hypothetical plum is not regulated by APHIS, and no petition would be submitted, no public comment period related to an APHIS determination would need to take place”, (2) explain how developers can obtain regulatory status (AIR process), and (3) term “nonregulated status” does not appear in Appendix 2; A second commenter stated, “Case Study #2: In Section VII Public Engagement, “a public comment period related to an APHIS petition is described. The commenter noted that the hypothetical plum is not regulated by APHIS and no petition would be submitted and, therefore, no public comment period related to an APHIS determination would need to take place.”

B. Comments for Consideration/Clarification as Part of Future Activities

Additional Case-Studies

One commenter stated that, by focusing only on clear-cut examples, the Proposed Update to the Coordinated Framework does not reflect current advancements or account for the likelihood that future technologies will likely fall far outside of the confines of current statutes. Another commenter recommended that agencies include, in their annual report, real-world case studies of regulatory assessments that were successful and timely as well as those that were not.

Agency designees for coordination and the Biotechnology Working Group

Two commenters pointed out that the Proposed Update to the Coordinated Framework did not identify agency designees or a mechanism for identifying such designees responsible for coordination under the Coordinated Framework. These commenters recommended careful consideration of options, such as explicitly designating interagency coordination as a primary responsibility of certain key employee(s) at all three agencies. One such commenter also suggested that this information could be provided on each agency’s website, or on a Coordinated Framework website such as the previous (now defunct) “U.S. Regulatory Agencies Unified Biotechnology Website”. Several commenters generally favored the formation of the Biotechnology WG to facilitate inter-agency communication, and encouraged the White House to provide sustained leadership encouraging interagency communication, coordination and cooperation. One commenter suggested that OSTP or Biotech Working Group (BWG) develop a “single point of contact” mechanism for an interested developer to request meetings, perhaps with the BWG or an Ombudsman within OSTP.

Definitions

One commenter recommended the use of common definitions of biotechnology across all agencies working under the Coordinated Framework. Another commenter suggested that EPA, FDA, and USDA apply the July 2015, EOP memorandum’s definition of “biotechnology products” within their regulations.

Engaging State Regulatory Partners

One commenter requested agencies to work closely with state regulatory partners and the agricultural stakeholder community to enhance continued alignment and improve communication between the federal, state, and agricultural stakeholders.

Future Updates to the Coordinated Framework

Expressing concern that the process for updating the Coordinated Framework thus far has lacked adequate public engagement, one commenter provided explicit recommendations on steps OSTP and agencies should take prior to making a decision on how to update the Coordinated Framework.

GE Insects

One commenter recommended establishing new regulations for EPA to review all techniques intended to work as pesticidal products in the bodies of insects whether such techniques involve genetic constructs or bacterial infection.

Genome Editing

Some comments recommended specific approaches for regulation of products derived from genome editing

- One of these commenters also asserted that it is critical for the NAS study to be completed and for agencies to formulate policies on genome editing after the risks of these technologies, if any, are identified.
- Another of these commenters believes FDA's definition of GE animal is process-based and, therefore, inconsistent with overarching principles in the Proposed Update to the Coordinated Framework. This commenter further argued gene editing does not fit within the Coordinated Framework or GFI 187.
- The Govt. of Canada encouraged continued transparency, and asked to be informed of regulatory developments re: genome editing and other future activities through the WTO notification process.

Improving Regulatory Processes

Several commenters asked agencies to implement a process to identify and improve the timeliness, efficiency, and predictability of regulatory processes, including ways to reduce redundant data requirements or review of products that agencies are familiar with. Overall, several commenters sought transparency of agency regulatory timelines, if they exist, e.g., PRIA timelines.

Commenters also emphasized the need for clear guidance on the scope of regulations, data requirements, regulatory processes, and bases of decision-making, not only for regulatory reviews of products entering the marketplace, but also for oversight of field trials and other regulatory activities.

One comment recommended more transparency with regard to the collaborative efforts across the agencies.

Arguing that the regulatory system lacks a process for quantitatively determining the efficacy and effectiveness of its regulations, one commenter recommended integrating appropriate and measurable metrics into both the Coordinated Framework review process as well as implementation of regulations.

Another commenter recommended that agencies develop a comprehensive and robust regulatory process to ensure full assessment and coordinated agency reviews of the combined impacts (environmental, social, ecological, and economic impacts) of biotechnology crops.

International Engagement and Trade Concerns

Some commenters also asked for greater involvement from and consultation with the regulated community, key governments, and the Office of the U.S. Trade Representative during the review and consideration of any future regulatory or policy initiatives to minimize potential disruptions to trade.

In addition, the Government of Canada, noting the integrated nature of U.S. and Canadian agricultural markets, emphasized the importance of predictable and transparent regulatory systems to facilitate trade and investment in innovation. This commenter recommended that any changes to U.S. biotechnology regulatory framework should be developed and implemented in a way that minimizes the potential for asynchronous approval for innovative agricultural products.

One commenter discussed various items described in the National Strategy, including international leadership and regulatory predictability as well as regulatory coherence/compatibility with key trading partners.

Levels of oversight

Commenters requested additional information on the level of oversight applied to different products. One of these commenters stated that the Proposed Update to the Coordinated Framework should clarify what is and what is not a regulated product, and to maintain this clarity as products of new technologies are developed. Another commenter recommended providing clear triggers for different levels of oversight based on risks associated with products, which the commenter believes would provide greater predictability for developers. Other commenters suggested that EPA and USDA are leaving open a regulatory gap when concurrent review of herbicides and herbicide resistant crops are not coordinated.

MOUs

One commenter stated the Proposed Update to the Coordinated Framework would be strengthened if it included examples of situations where the cited MOU has been utilized in practice to increase regulatory efficiency. This commenter believes agencies should utilize MOUs to enable sharing of data and data reviews to increase efficiency of regulatory reviews, but cautioned that shared data reviews should not become a barrier to timely and predictable decision-making by any one agency.

Regulatory Science

One commenter highlighted the need for research to inform contamination prevention strategies, and urged the agencies to include in their research plans a process to analyze the long-term direct and indirect environmental as well as economic effects of GE contamination.

Risk/safety assessments

Commenters recommended providing information on the specific risks addressed by each agency and descriptions of how those risks are assessed in product evaluations, including risk methodologies and tools. Commenters believe such information will be helpful not only for product developers, especially small businesses, but also to highlight for the general public the robustness of the regulatory process.

Strengthening Public Communications

Several commenters expressed a belief that the government can help improve public understanding and acceptance of biotechnology, and urged agencies to be more proactive and increase public engagement efforts, making stakeholder outreach a regular and ongoing activity. Commenters noted it is imperative for agencies to communicate with industry stakeholders, other federal agencies, and international trading partners in order to help stakeholders understand the regulatory system; defend agencies' science-based decisions and safety assessments; make regulatory actions more accessible and understandable; and solicit feedback on the functioning of the regulatory system and its impacts on stakeholders. In this context, one commenter noted the value of USDA's BRS' Annual Stakeholder meeting, and recommended adopting a similar annual or bi-annual meeting of EPA, FDA, and USDA to promote coordination, communication, and regulatory transparency.

In addition, one commenter asked agencies to consider mechanisms such as social media and email notices to correct important inaccuracies and misinterpretations about agency decisions and the regulatory system that are reported in the media.

Another commenter encouraged OSTP to oversee a public education period to provide the public with clear, objective information assessing the relative risks and benefits of different approaches to regulation (product-based, process-based, hybrid of the two, or other alternative approach), followed by opportunity for stakeholders to provide comment on the merits of the various regulatory approaches.

Timeline for inter-agency coordination

Two comments addressed timelines for regulatory reviews and work plan for current and future agency actions. One commenter expressed concern that regulatory processes within the coordinated framework may lead to stalled or incomplete reviews, unless specific timetables are spelled out. This commenter asked whether, under the Coordinated Framework, an agency could hold up the regulatory review process, citing an example of how consultations on endangered species assessment have impacted EPA's assessment progress, and how long an agency would wait for another agency to complete its assessment. Another commenter urged agencies to provide a timeline of "actual and contemplated GE-related actions" including their inter-relationship. The commenter believes such information will help to improve transparency, stakeholder engagement, and streamlining of inter-agency actions, and urged agencies to follow-

through on the statement in the Proposed Update to the Coordinated Framework that the annual report could include “a concrete list of regulatory and other activities and timeframes.

III. Other Comments

- Comments related to FDA’s voluntary consultation process; consideration of GE under the GRAS framework, including
 - recommendation to consider GE under food additives framework, requiring mandatory pre-market review and safety assessment and/or mandatory labeling; and
 - recommendation for FDA to consider ways to transition away from being event-specific since unintended hazards in food and feed are not more likely to arise in biotechnology crops than in crops developed by other processes.
- Comments about FDA regulation of GE animals (and GFI 187), generally, and specifically on what the commenters considered to be FDA’s “failure to ensure food safety and environmental safety in its review” of GE salmon.
- Comment related to FDA regulatory processes for reviewing novel animal feed ingredients derived from “genetically modified microorganisms.”
- Comments recommending that agencies require long-term, independent safety testing; apply the precautionary principle for mandatory pre-market approval; require mandatory labeling; reduce corporate influence; and establish liability for GE contamination and protect organic farming.
- Comment expressing strong concern about the prospect of genome editing for human reproduction, and recommending that the Coordinated Framework call on agencies to refrain from any human germline modification.
- Comments about what respondents considered to be a lack of opportunity for proper process and participation in the three public meetings.
- Two comments about low-level presence:
 - One commenter asserts that Proposed Update to the Coordinated Framework “fails to address appropriate government oversight of biotech-enhanced traits that have functionally different output characteristics than their conventional counterparts (e.g., Enogen® corn containing alpha amylase) that can affect nutritional, compositional or other end-use properties, thereby making their presence in the food or feed system inappropriate above certain threshold levels.” This commenter recommended the development of a U.S. regulatory policy for the low-level presence of genetically engineered products in food, feed and seeds.
 - Another commenter believes FDA’s New Protein Consultations are an important aspect of the U.S. approach to inadvertent, intermittent, low-level presence of proteins in the food supply.

- Comments related to USDA's implementation of the National Bioengineered Food Disclosure Law.

Appendix 3: Definitions of Key Terms

Below are agency-specific key terms relevant to the regulation of biotechnology products.

NOTE: The regulatory agency using a particular term is indicated in parentheses following the term. In addition, the definitions are derived from a variety of sources, including explicit language from statutes and regulations, paraphrased language, language from regulatory preambles, and, in one instance, language from an executive order.

Animal Health Protection Act

- *Livestock* (USDA):¹²³ farm-raised animals, including horses, cattle, bison, sheep, goats, swine, cervids, poultry and others, including farm-raised fish.

FD&C Act: Federal Food, Drug, and Cosmetic Act

- *Animal food* (FDA): See “*food*”
- *Cosmetic* (FDA):¹²⁴
 - Articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance; and
 - Articles intended for use as a component of any such articles; except that such term shall not include soap.
- *Device* (FDA) (referred to in this document as “*Medical Device*”):¹²⁵ An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory
 - which is:
 - Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them;
 - Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or
 - Intended to affect the structure or any function of the body of man or other animals; and
 - which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.
- *Drug* (FDA):¹²⁶

¹²³ Animal Health Protection Act, 7 U.S.C. § 8302.

¹²⁴ Section 201(i) of the FD&C Act [21 U.S.C. § 321(i)].

¹²⁵ Section 201(h) of the FD&C Act [21 U.S.C. § 321(h)].

¹²⁶ Section 201(g)(1) of the FD&C Act [21 U.S.C. § 321(g)(1)].

- Articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them;
- Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;
- Articles (other than food) intended to affect the structure or any function of the body of man or other animals; and
- Articles intended for use as a component of any article specified in a clause above.

A food or dietary supplement for which a claim, subject to sections 403(r)(1)(B) and 403(r)(3) of the FD&C Act or sections 403(r)(1)(B) and 403(r)(5)(D) of the FD&C Act, is made in accordance with the requirements of section 403(r) is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 403(r)(6) of the FD&C Act is not a drug under clause (C) (articles other than food intended to affect the structure or any function of the body of man or other animals) solely because the label or the labeling contains such a statement.

- *Food* (FDA):¹²⁷ Articles used for food or drink for man or other animals; chewing gum; and articles used for components of any such article.
- *Food additive* (FDA):¹²⁸ Any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include:
 - A pesticide chemical residue in or on a raw agricultural commodity or processed food; or
 - A pesticide chemical; or
 - A color additive; or
 - Any substance used in accordance with a sanction or approval granted prior to September 6, 1958, pursuant to this chapter, the Poultry Products Inspection Act [21 U.S.C. § 451 et seq.] or the Meat Inspection Act of March 4, 1907, as amended and extended [21 U.S.C. § 601 et seq.]; or
 - A new animal drug; or
 - An ingredient in, or intended for use in, a dietary supplement.

¹²⁷ Section 201(f) of the FD&C Act [21 U.S.C. § 321(f)].

¹²⁸ Section 201(s) of the FD&C Act [21 U.S.C. § 321(s)].

- *New animal drug* (FDA):¹²⁹ any drug intended for use for animals other than man, including any drug intended for use in animal feed but not including such animal feed,--
 - (1) The composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof; except that such a drug not so recognized shall not be deemed to be a "new animal drug" if at any time prior to June 25, 1938, it was subject to the Food and Drug Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or
 - (2) The composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions,

Provided that any drug intended for minor use or use in a minor species that is not the subject of a final regulation published by the Secretary [of Health and Human Services] through notice and comment rulemaking finding that the criteria of paragraphs (1) and (2) have not been met (or that the exception to the criterion in paragraph (1) has been met) is a new animal drug.

- *New drug* (FDA):¹³⁰
 - Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or
 - Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.
- *Safe* (EPA):¹³¹ The safety standard under the FD&C Act sections 408(b) and (c) defines "safe" as "There is a reasonable certainty that no harm will result from aggregate

¹²⁹ Section 201(v) of the FD&C Act [21 U.S.C. § 321(v)].

¹³⁰ Section 201(p) of the FD&C Act [21 U.S.C. § 321(p)].

¹³¹ Sections 408(b)(2)(A)(ii) and 408(c)(2)(A)(ii) of the FD&C Act [21 U.S.C. §§ 346a(b)(2)(A)(ii) and 346a(c)(2)(A)(ii)].

exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.”

FIFRA: Federal Insecticide, Fungicide, and Rodenticide Act

- *Animal* (EPA):¹³² Under FIFRA section 2(q), an animal is defined as “all vertebrate and invertebrate species, including but not limited to man and other mammals, birds, fish and shellfish.
- *Environment* (EPA):¹³³ Under FIFRA section (2)(j), the term environment “[i]ncludes water, air, land and all plants and man and other animals living therein, and the interrelationships which exist among these.”
- *Inert ingredient* (EPA):¹³⁴ At 40 C.F.R. § 174.3, for plant-incorporated protectants only an inert ingredient is defined as “any substance, such as a selectable marker, other than the active ingredient, where the substance is used to confirm or ensure the presence of the active ingredient, and includes the genetic material necessary for the production of the substance, provided that genetic material is intentionally introduced into a living plant in addition to the active ingredient.”
- *Living plant* (EPA):¹³⁵ At 40 C.F.R. § 174.3, a living plant is defined as “a plant, plant organ or plant part that is alive, viable, or dormant. Examples include, but are not limited to, seeds, fruits, leaves, roots, stems, flowers and pollen.”
- *Microorganism* (EPA):¹³⁶ prokaryotes, algae, fungi, protists, viruses, and virus-like particles.
- *Pesticide* (EPA):¹³⁷ Under FIFRA section 2(u), the term pesticide means, in part, “(1) any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, (2) any substance or mixture of substances intended for use as a plant regulator, defoliant or desiccant, and (3) any nitrogen stabilizer. . .”
- *Pesticidal substance* (EPA):¹³⁸ At 40 C.F.R. §174.3, a pesticidal substance means “a substance that is intended to be produced and used in a living plant, or in the produce thereof, for a pesticidal purpose, during any part of a plant’s life cycle (*e.g.*, in the embryo, seed, seedling, mature plant).”
- *Plant* (EPA):¹³⁹ Under FIFRA regulations at 40 C.F.R. §174.3, plant is defined to mean “[a]n organism classified using the 5-kingdom classification of Whittaker in the kingdom

¹³² Section 2(d) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) [7 U.S.C. § 136(d)].

¹³³ Section 2(j) of FIFRA [7 U.S.C. § 136(j)].

¹³⁴ 40 C.F.R. § 174.3.

¹³⁵ 40 C.F.R. § 174.3.

¹³⁶ 40 C.F.R. § 172.43.

¹³⁷ Section 2(u) of FIFRA [7 U.S.C. § 136(u)].

¹³⁸ 40 C.F.R. § 174.3.

¹³⁹ 40 C.F.R. § 174.3.

Plantae. This includes but is not limited to, bryophytes such as mosses, pteridophytes such as ferns, gymnosperms such as conifers, and angiosperms such as most major crop plants.”

- *Plant-incorporated protectant* (EPA):¹⁴⁰ At 40 C.F.R. § 174.3, “a pesticidal substance that is intended to be produced and used in a living plant, or in the produce thereof, and the genetic material necessary for production of such a pesticidal substance. It also includes any inert ingredient contained in the plant, or produce thereof.”
- *Unreasonable adverse effects on the environment* (EPA):¹⁴¹ At FIFRA section 2(u)(bb), “[a]ny unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide, or a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard in section 408 of the Federal Food, Drug, and Cosmetic Act.”
- *Weed* (EPA):¹⁴² Under FIFRA section 2(u)(cc), the term “weed” means “any plant which grows where not wanted.”

PPA: Plant Protection Act

- *Antecedent organism* (USDA):¹⁴³ An organism that has already been the subject of a determination of nonregulated status by APHIS under 7 C.F.R. § 340.6, and that is used as a reference for comparison to the regulated article under consideration under these regulations.
- *Extension process* (USDA):¹⁴⁴ The process where APHIS extends a determination of nonregulated status to additional regulated articles based on similarity to an antecedent organism. This process is used when the new regulated article differs negligibly, from a safety standpoint, from others that have already been reviewed and subject to determinations of nonregulated status. The aim of making comparisons between regulated articles and their antecedent organisms is to ensure that the new regulated articles in question raise no serious new issues meriting separate review under the petition process.
- *Genetic engineering, GE* (USDA):¹⁴⁵ The genetic modification of organisms by recombinant DNA techniques.
- *Nonregulated status* (USDA):¹⁴³ Refers to the conclusion reached by APHIS when a genetically engineered organism, previously determined to be a regulated article, has

¹⁴⁰ 40 C.F.R. § 174.3.

¹⁴¹ Section 2(u)(bb) of FIFRA 2(u)(bb) [7 U.S.C. § 136(bb)].

¹⁴² Section 2(u)(cc) of FIFRA [7 U.S.C. § 136(cc)].

¹⁴³ 7 C.F.R. § 340.6.

¹⁴⁴ 7 C.F.R. § 340.6(e).

¹⁴⁵ 7 C.F.R. § 340.1.

been determined to not pose a risk as a plant pest and is no longer subject to the regulations at 7 C.F.R. Part 340.

- *Noxious weed* (USDA):¹⁴⁶ Any plant or plant product that can directly or indirectly injure or cause damage to crops (including nursery stock or plant products), livestock, poultry, or other interests of agriculture, irrigation, navigation, the natural resources of the United States, the public health, or the environment.
- *Permit* (USDA):¹⁴⁷ A written permit issued by the Administrator, for the introduction of a regulated article under conditions determined by the Administrator, not to present a risk of plant pest introduction.
- *Petition process* (USDA):¹⁴⁸ The process where a person may petition the agency that a particular regulated article is unlikely to pose a plant pest risk, and, therefore, is no longer regulated under the plant pest provisions of the Plant Protection Act or the regulations at 7 C.F.R. Part 340; The petitioner is required to provide information under 7 C.F.R. § 340.6(c)(4) related to plant pest risk that the agency may use to determine whether the regulated article is unlikely to present a greater plant pest risk than the unmodified organism.
- *Plant* (USDA):¹⁴⁹ Any plant (including any plant part) for or capable of propagation, including a tree, a tissue culture, a plantlet culture, pollen, a shrub, a vine, a cutting, a graft, a scion, a bud, a bulb, a root, and a seed.
- *Plant* (USDA):¹⁵⁰ Any living stage or form of any member of the plant kingdom 3 including, but not limited to, eukaryotic algae, mosses, club mosses, ferns, angiosperms, gymnosperms, and lichens (which contain algae) including any parts (*e.g.*, pollen, seeds, cells, tubers, stems) thereof, and any cellular components (*e.g.*, plasmids, ribosomes, etc.) thereof.
- *Organism* (USDA):¹⁵¹ Any active, infective, or dormant stage or life form of an entity characterized as living, including vertebrate and invertebrate animals, plants, bacteria, fungi, mycoplasmas, mycoplasma-like organisms, as well as entities such as viroids, viruses, or any entity characterized as living, related to the foregoing.
- *Regulated article* (USDA):¹⁵⁰ Any organism which has been altered or produced through genetic engineering, if the donor organism, recipient organism, or vector or vector agent belongs to any genera or taxa designated in 7 C.F.R. § 340.2 and meets the definition of plant pest, or is an unclassified organism and/or an organism whose classification is unknown, or any product which contains such an organism, or any other organism or product altered or produced through genetic engineering, which the Administrator determines is a plant pest or has reason to believe is a plant pest. Excluded are recipient

¹⁴⁶ Section 403(10) of the Plant Protection Act (PPA), 7 U.S.C. § 7702.

¹⁴⁷ 7 C.F.R. § 340.1.

¹⁴⁸ 7 C.F.R. § 340.6(c).

¹⁴⁹ Section 403(13) of the PPA, 7 U.S.C. § 7702.

¹⁵⁰ 7 C.F.R. § 340.1.

¹⁵¹ 7 C.F.R. § 340.1.

microorganisms which are not plant pests and which have resulted from the addition of genetic material from a donor organism where the material is well characterized and contains only non-coding regulatory regions.

- *Release into the environment* (USDA):¹⁵² The use of a regulated article outside the constraints of physical confinement that are found in a laboratory, contained greenhouse, or a fermenter or other contained structure.

PHS Act: Public Health Service Act

- *Biological product* (FDA):¹⁵³ A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

TSCA: Toxic Substance Control Act

- *Microorganism* (EPA):¹⁵⁴ “An organism classified, using the 5-kingdom classification system of Whittaker, in the kingdoms Monera (or Procaryotae), Protista, Fungi, and the Chlorophyta and the Rhodophyta of the Plantae, and a virus or virus-like particle.”
- *New microorganism* (EPA): “New microorganisms for which manufacturers and importers are required to report under section 5(a)(1)(A) of TSCA are those that are intergeneric.”¹⁵⁵ “Intergeneric microorganism” means a “microorganism that is formed by the deliberate combination of genetic material originally isolated from organisms of a different taxonomic genera.”¹⁵⁶ “In the case of chemically synthesized genes, the Agency will follow the same principle,”¹⁵⁷ meaning EPA also interprets “intergeneric” to include microorganisms formed by the introduction of chemically synthesized genetic material that is not identical to that found in the subject genus.
- *Unreasonable risk of injury to health or the environment* (EPA):¹⁵⁸ “A chemical substance that the Administrator concludes, without consideration of costs or other nonrisk factors, may present an unreasonable risk of injury to health or the environment because of a potential hazard and a potential route of exposure under the conditions of use, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant by the Administrator.”

¹⁵² 7 C.F.R. § 340.1.

¹⁵³ Section 351(i)(1) of the Public Health Service (PHS) Act [42 U.S.C. § 262(i)(1)].

¹⁵⁴ 40 C.F.R. § 725.3.

¹⁵⁵ 40 C.F.R. § 725.1.

¹⁵⁶ 40 C.F.R. § 725.3.

¹⁵⁷ 1986 Coordinated Framework, 51 FR at 23325.

¹⁵⁸ 15 U.S.C. § 2604(b)(1)(B)(i).

Virus-Serum-Toxin Act¹⁵⁹

- *Veterinary Biologic* (USDA):¹⁶⁰ “Biological products – the term biological products, also referred to in this subchapter as biologics, biologicals, or products, shall mean all viruses, serums, toxins (excluding substances that are selectively toxic to microorganisms, *e.g.*, antibiotics), or analogous products at any stage of production, shipment, distribution, or sale, which are intended for use in the treatment of animals and which act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response. The term ‘biological products’ includes but is not limited to vaccines, bacterins, allergens, antibodies, antitoxins, toxoids, immunostimulants, certain cytokines, antigenic or immunizing components of live organisms, and diagnostic components, that are of natural or synthetic origin, or that are derived from synthesizing or altering various substances or components of substances such as microorganisms, genes or genetic sequences, carbohydrates, proteins, antigens, allergens, or antibodies.”

Other Key Terms (Identified by Agency)

- *Invasive Species* (USDA):¹⁶¹ As per Executive Order -- Safeguarding the Nation from the Impacts of Invasive Species, 'Invasive species' means, with regard to a particular ecosystem, a non-native organism whose introduction causes or is likely to cause economic or environmental harm, or harm to human, animal, or plant health.

¹⁵⁹ 21 U.S.C. §§ 151-159.

¹⁶⁰ 9 C.F.R. § 101.2.

¹⁶¹ Executive Order -- Safeguarding the Nation from the Impacts of Invasive Species (December 5, 2016).