

The Coordinated Framework for the Regulation of Biotechnology

*Plan for Regulatory Reform under the
Coordinated Framework for the Regulation
of Biotechnology*

May 2024

*The U.S. Department of Agriculture
The U.S. Environmental Protection Agency
The U.S. Food and Drug Administration*

TABLE OF CONTENTS

| | |
|--|----------|
| Introduction..... | 3 |
| Background..... | 4 |
| Regulatory Plan | 5 |
| A. Modified Plants..... | 5 |
| B. Modified Animals..... | 9 |
| C. Modified Microorganisms..... | 10 |
| D. Human Drugs, Biologics, and Medical Devices | 12 |
| E. Cross-cutting Issues | 15 |

INTRODUCTION

On September 12, 2022, President Biden issued [Executive Order 14081](#), “Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure Bioeconomy,” with the goal of accelerating biotechnology innovation and growing America’s bioeconomy across multiple sectors, including health, agriculture, and energy. Among other objectives, the executive order aims to support the safe use of biotechnology products by clarifying and streamlining regulations in service of a science- and risk-based, predictable, efficient, and transparent regulatory system. The executive order directs the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), and the United States Department of Agriculture (USDA) to:

- identify any regulatory ambiguities, gaps, or uncertainties in the [Coordinated Framework for Regulation of Biotechnology](#) (“Coordinated Framework”) through engaging with developers and stakeholders and through horizon scanning for novel biotechnology products;
- provide plain-language information on the regulatory roles, responsibilities, and processes of each agency;
- provide a plan with processes and timelines to implement regulatory reform, including identification of regulations and guidance documents that can be updated, streamlined, or clarified, and identification of potential new guidance or regulations, where needed;
- build on the Unified Website for Biotechnology Regulation by further providing plain-language information on the regulatory roles, responsibilities, and processes of each agency, and by enabling developers of biotechnology products to submit inquiries about a particular product and promptly receive a single, coordinated response that provides, to the extent practicable, information and, when appropriate, informal guidance regarding the process that the developers must follow for federal regulatory review.

The executive order describes biotechnology as “technology that applies to and/or is enabled by life sciences innovation or product development.” Biotechnology products include organisms (like plants, animals, and microbes) developed through genetic engineering or the targeted or in vitro manipulation of genetic information, some products derived from such organisms, as well as products produced via cell-free synthesis.

Consistent with the executive order, EPA, FDA, and USDA are issuing this plan to implement regulatory reform, including identification of regulations and guidance documents that can be updated, streamlined, or clarified, and identification of potential new guidance or regulations, where needed.

This report incorporates public input about regulatory ambiguities, gaps, uncertainties, and inefficiencies in the Coordinated Framework obtained in response to a [Request for Information](#) issued on December 15, 2022. Stakeholders commented on the regulation of modified plants, modified animals, and modified microorganisms that fall under the Coordinated Framework, regulation of human therapeutics, and four cross-cutting topics.

Stakeholders requested greater clarity on and assistance with the regulation of biotechnology products that fall under the Coordinated Framework. Commenters also suggested increased harmonization of policies, processes, and requirements, and coordination between the regulatory agencies. Commenters expressed a variety of concerns and recommendations for regulatory reform or revision for specific product categories (plants, animals, microorganisms). There were comments and recommendations specific to each agency and general across all agencies, including requests for streamlining regulatory processes, reducing potentially duplicative regulation, and filling regulatory gaps. Commenters also

expressed concern that the regulatory agencies are under-resourced and expressed support for additional resources and training for the agencies and their staff. A more [detailed summary of comments](#) received on the Request for Information can be found on the Unified Website for Biotechnology Regulation.

This plan provides a roadmap for actions the agencies will take, individually and collaboratively, to improve regulatory clarity, streamline regulatory oversight, reduce regulatory redundancies and gaps, and increase regulatory coordination for specific product categories and across the Coordinated Framework.

BACKGROUND

In 1986, the Office of Science and Technology Policy (OSTP) issued the [Coordinated Framework for Regulation of Biotechnology](#) (“Coordinated Framework”) in response to concerns about whether the “regulatory framework that pertained to products developed by traditional genetic manipulation techniques was adequate for products obtained with the new techniques.” The Coordinated Framework outlined the federal regulatory policy for biotechnology products and federal agency oversight responsibilities to protect health and the environment while advancing innovation.

In 1992, OSTP issued an [update](#) to the Coordinated Framework that set forth a risk-based, scientifically sound approach for the oversight of activities that introduce biotechnology products into the environment (57 FR 6753). The update reaffirmed that federal oversight should focus on the characteristics of the product, the environment into which it is being introduced, and the intended use of the product, rather than the process by which the product is created.

The Coordinated Framework contributed to decades of development and commercialization of biotechnology products with applications in medicine, agriculture, energy, biomanufacturing, and environmental protection. It also contributed to the growth of a large and competitive biotechnology sector in the United States and around the world.

Advances in science and technology have continued to alter the biotechnology landscape since the issuance of the 1986 Coordinated Framework and associated 1992 update. Consequently, in 2015, the Executive Office of the President issued a [memorandum](#) directing EPA, FDA, and USDA to update the Coordinated Framework to facilitate appropriate federal oversight of biotechnology products and increase transparency, while continuing to provide a framework for advancing innovation. The Federal government subsequently published a [National Strategy for Modernizing the Regulatory System for Biotechnology](#) in 2016; and an [Update to the Coordinated Framework in 2017](#). The 2017 update lists the offices within each agency or agencies that may have regulatory responsibilities for a given biotechnology product category and provides relevant coordination across the agencies. It also describes memoranda of understanding (MOUs) among the agencies and the types of products and information that are within the scope of each MOU.

In 2019, [Executive Order 13874](#), Modernizing the Regulatory Framework for Agricultural Biotechnology Products, recognized that advances in biotechnology have the potential to revolutionize agriculture, enhance rural prosperity, and improve the quality of American lives. This executive order directed agencies to take additional steps to modernize the regulatory framework. Since 2019, the regulatory agencies have continued to revise and update their biotechnology regulations and guidances.

The 2022 executive order continues bipartisan efforts to update and streamline regulation of biotechnology products that fall under the Coordinated Framework as biotechnology advances.

REGULATORY PLAN

The agencies have identified five areas of biotechnology product regulation where these actions will focus:

- A.** Modified plants
- B.** Modified animals
- C.** Modified microorganisms
- D.** Human drugs, biologics, and medical devices
- E.** Cross-cutting issues

A. MODIFIED PLANTS

Commenters expressed various agency-specific and cross-agency concerns about the regulation of modified plants and plant products, including: cumbersome and lengthy regulatory processes; the scope of “plant-incorporated protectants” (PIPs); lack of harmonization of approaches to the regulation of genome edited plants and new varieties of previously reviewed plants; lack of alignment of timelines for reviews of products subject to regulation by more than one agency; food crops engineered to produce substances that could cause food safety concerns if they inadvertently enter the general food supply; duplicative regulation of genetically modified plants; and a need for recognition by agencies of each other’s expertise in order to promote predictability, reduce redundancy, and enable synchronous agency decisions.

1. Agencies will identify ways to streamline review processes.

- a. USDA will identify ways to streamline its Regulatory Status Review (RSR) process.** Modified plants that do not meet the criteria for exemption from USDA regulations have an opportunity for a regulatory off-ramp through the RSR process. To improve the predictability of this process (which is important for developers making business plans and decisions), in fiscal year (FY) 2024, USDA will undertake a review of the RSR process to identify process improvements that will bring processing times into greater alignment with the target timeframes specified in its biotechnology regulations. For example, to reduce the time it takes to prepare plant biology documents and analyses of how modifications may alter a plant’s biological function, USDA has updated its RSR guidance to allow developers to submit publicly available materials related to plant biology and mechanisms of action, engaged the National Agricultural Library to deliver staff training related to literature searches and support development of standard search queries, and received approval to test a narrow language learning model to facilitate the rapid identification of literature to support regulatory reviews. Following the FY24 review, USDA will continue implementing process improvements and track progress in shortening the time taken to complete reviews until it reaches full alignment with the timeframes specified in the biotechnology regulations.
- b. EPA will identify ways to streamline and ensure consistency across its PIP registration reviews.** To improve the quality of materials received and the predictability of reviews of PIP registration applications under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), EPA is developing guidance documents on common data needs for PIPs for each of the three components of the risk assessment: molecular characterization,

human health assessment, and ecological assessment. Providing clear guidance as to what data are typically needed, and when scientific rationale could likely be used in place of data, will result in a more consistent, streamlined review process. EPA will also develop internal guidance for PIPs related to technical screen checklists, study evaluation templates, and risk assessment templates to ensure consistency across reviews.

c. FDA intends to develop procedural guidance for participants in its voluntary consultation program as resources allow.

The guidance would provide clarity for stakeholders to make for a more efficient and timely voluntary consultation process. This guidance would help stakeholders better understand the food safety issues considered in the voluntary consultation process and thereby lead to higher quality submissions from program participants. This guidance may also provide business process improvements that enable FDA to respond to consultation submissions in a more timely way.

2. USDA will streamline its permitting process and update its user guides.

Under USDA's revised regulations, modified plants that do not meet the criteria for regulatory exemption and that have not successfully completed the RSR process require a permit for import, interstate movement, and environmental release. To improve consistency in oversight, the revised regulations adopted a single method for authorizing regulatory activities using a permitting process. Separately, USDA adopted a new web-based permitting system for a variety of different products, including but not limited to biotechnology products. Collectively, these two actions added administrative steps related to biotechnology permit issuances for external and internal users, increasing processing times and impacting the predictability of the permitting process. To address these issues, beginning in the first quarter of FY24, USDA will take the following actions:

- a. In consultation with EPA and FDA, USDA will explore eliminating interstate movement permits for certain plants** or establishing alternative import and interstate movement permit categories for certain plants with streamlined processes and permit conditions, while retaining inspection and record keeping requirements.
- b. USDA will streamline permit application reviews** to remove identified redundancies within its permitting process, revise its Confidential Business Information review process, and conduct risk-based reviews of Standard Operating Procedures for which USDA has established standard supplemental permit conditions, including all interstate movement and importation permits for plants and for environmental releases for familiar crops (e.g., corn, soybean, cotton, potato, tomato, canola, and alfalfa) and traits. USDA will also consider issuing multi-year permits for all interstate movement and importation permits for plants and for environmental releases for familiar crops (e.g., corn, soybean, cotton, potato, tomato, and alfalfa) and traits.
- c. USDA will streamline Supplemental Permit Conditions** to ensure USDA assigns permit conditions that meet USDA protection goals, are consistent among developers, and provide concise, plain-language requirements. USDA is reviewing and revising current standard supplemental permit conditions for all movement types (importation, interstate movement, and environmental release). USDA will communicate key changes to stakeholders and finalize its review and revisions during FY24.

- d. **USDA will post updated and new user-friendly permitting guidance documents** for product developers in FY24, including:
 - 1. an update to the *Permit User Guide* to align with USDA's revised regulations and Animal and Plant Health Inspection Service's (APHIS') eFile permitting system; and
 - 2. a final *Guide to Submitting Data for Reports and Notices* that will provide information and instructions for permit holders on submitting reports and notices to maintain compliance with USDA regulations during regulated activities.

3. EPA and USDA will clarify and streamline PIP regulation.

a. **EPA recently implemented a Final Rule exemption for certain PIPs from FIFRA regulation.**

EPA finalized its proposal to exempt from FIFRA and the Federal Food, Drug, and Cosmetic Act (FFDCA) certain PIPs that are created in plants using newer technologies. EPA's rule allows certain PIPs to be exempt when those PIPs 1) meet EPA safety requirements, and 2) could have otherwise been created through conventional breeding. The rule also includes a process through which developers of PIPs, based on sexually compatible plants created using newer technologies, submit either a self-determination letter or request for EPA confirmation that their PIP meets the criteria for exemption. EPA has developed [online resources](#) for developers. These include two webinars describing details of the rule and how to navigate the submission process and examples that clarify the scope of the exemptions. EPA anticipates that these outreach activities will especially benefit smaller developers who may not have interacted with the agency in the past but who are also likely to have products that would qualify for the new exemptions.

b. **EPA will update existing guidance on small-scale field testing of PIPs.**

EPA plans to update existing guidance on small scale testing of PIPs. Current guidance (PRN 2007-2) describes how EPA's regulations on testing at or below 10 acres of land apply to field testing of PIPs. Current guidance, issued in 2007, indicates that, as for most other types of pesticides, testing of PIPs at small-scale (i.e., ≤10 acres) is presumed not to require an Experimental Use Permit so long as any food or feed crops involved in, or affected by, such tests are destroyed or consumed only by experimental animals unless a tolerance or exemption from tolerance has been established for residues of the pesticide. Given that PIPs, unlike other types of pesticides, can spread in the environment and enter the food supply, e.g., through gene flow from the test field to crops in surrounding fields, the 2007 guidance also recommended the use of additional containment measures to limit the potential for PIPs to move from the trial plot. In response to changes in the U.S. regulatory structure, EPA's new guidance would update the agency's approach, e.g., incorporate USDA's containment measures and modify, as necessary, the list of containment measures intended to reduce the probability for PIP residues to enter the food and feed supply from small scale field tests. As part of this effort, EPA and USDA will work together to facilitate harmonization of regulatory requirements for small-scale field trials of PIPs.

c. **USDA will clarify its exemption of modified plants containing PIPs.**

To minimize duplicative regulation of products that are subject to EPA pesticide regulations, in FY24 USDA will clarify its exemption from permitting requirements for

modified plants containing PIPs that are registered by EPA as pesticides and, in consultation with EPA, will explore additional mechanisms for minimizing duplicative regulation of such products.

d. EPA intends to address the scope of plant regulator PIPs.

As defined by EPA's FIFRA statute, plant regulators are "any substance or mixture of substances intended, through physiological action, for accelerating or retarding the rate of growth or rate of maturation or for otherwise altering the behavior of the plant or the produce thereof." In response to requests from developers, EPA intends to address the scope of plant regulator PIPs.

4. Genome edited plants. EPA, FDA, and USDA intend to clarify their regulatory approaches to genome edited plants and ensure their regulatory approaches are risk-proportionate.

a. EPA recently implemented a final rule exemption for certain PIPs from FIFRA regulation, as discussed above.

b. FDA recently issued "[Guidance for Industry: Foods Derived from Plants Produced Using Genome Editing](#)." This final [guidance](#) clarifies FDA's current thinking on the safety and regulatory status of foods derived from genome edited plant varieties in accordance with its 1992 policy on foods from new plant varieties. FDA recognizes the interest in using genome editing to produce new plant varieties. This guidance will help developers understand the types of food safety issues they should consider when developing new varieties. The guidance will also describe how developers can voluntarily interact with FDA prior to marketing foods from their new varieties.

c. USDA and EPA will solicit feedback on additional modifications in plants that can be exempt from their respective regulations.

USDA will consider comments on a recently published [notice](#) on additional modifications that plants, including polyploid plants, can contain and be exempt from its regulations, based on publicly available scientific information describing advances in conventional breeding techniques. EPA will similarly issue a notice to solicit feedback to identify new categories of PIPs that could meet the FIFRA and FFDCa statute requirements for exemption that could be added to the list of exempt genetically engineered PIPs in future rulemakings. Identifying additional modifications that are eligible for exemption because they are achievable through conventional breeding would improve regulatory alignment within the U.S. government.

5. Streamline update of the List of Bioengineered Foods.

USDA will streamline the process to update the List of Bioengineered Foods maintained in accordance with the National Bioengineered Food Disclosure Standard. USDA-Agricultural Marketing Service (AMS) works with USDA-Animal and Plant Health Inspection Service (APHIS), FDA, and EPA to identify foods that meet the definition of a bioengineered food. This list helps identify foods or ingredients that may be required to be labeled bioengineered. USDA will publish a request for information rather than an advance notice of proposed rulemaking to start each cycle of list updates to accelerate the rulemaking process, while continuing to allow for critical stakeholder input and feedback.

6. FDA and USDA intend to collaborate to consider mechanisms for stewardship of food crops engineered to produce substances that could cause food safety concerns, or other food crops where stewardship may be important, if they inadvertently enter the food supply.

USDA and FDA have noted an increased interest in using genetic engineering to produce, in food crops, ingredients intended for specific food uses that may pose food safety issues if they enter the general food supply (e.g., allergenic ingredients not previously produced by those crops) as well as other food crops where stewardship may be important. This is an issue almost unique to genetic engineering because of its ability to transfer genes among distantly related organisms (e.g., between the plant and animal kingdoms). The Coordinated Framework did not explicitly address this subset of genetically engineered food crops. FDA and USDA intend to consider mechanisms for stewardship of such crops to ensure they are directed toward their intended uses and to minimize, where relevant, the possibility that material from the crops inadvertently enters the general food supply. Such mechanisms may be led by developers or third parties with advice from USDA and FDA, as appropriate, and could be applicable to other situations in the future if relevant.

B. MODIFIED ANIMALS

Commenters stressed the importance of providing clarity about the regulatory process for modified agricultural animals that fall under the Coordinated Framework, noted the ongoing discussions between FDA and USDA, and encouraged the agencies to bring closure to discussions, noting the importance of streamlining rather than complicating the regulatory process, although commenters differed in their preferred outcome. Commenters also requested that FDA and USDA provide information on principles and process for implementing regulatory oversight of cultured animal cell foods per their March 2019 Formal Agreement. The regulatory process for modified insects and other invertebrates also remains unclear and duplicative in some circumstances.

1. FDA and USDA recently signed a Memorandum of Understanding (MOU) on information sharing and regulatory cooperation on heritable intentional genomic alterations in animals that are also subject to USDA oversight.

It establishes policies and procedures to enhance the exchange of information between the agencies; describes the regulatory roles of the agencies; and promotes coordination of regulatory responsibilities. It does not change or add regulatory requirements for developers.

2. FDA recently issued two companion guidances on heritable intentional genomic alterations (IGAs) in animals.

a. Guidance for Industry #187A, “Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach,” is a final guidance describing FDA’s general approach to the oversight of heritable IGAs in animals.

Under this approach, the FDA may exercise enforcement discretion and not expect people or companies developing certain types of IGAs in animals to submit an application or get approval before marketing their product.

b. Guidance for Industry #187B, “Heritable Intentional Genomic Alterations in Animals: The Approval Process,” is a draft revised guidance that describes how the FDA approval process applies to heritable IGAs in animals.

The FDA is issuing GFI #187B as a draft guidance to solicit comments that will enable the agency to update, and make as efficient as possible, the approval process for IGAs in animals.

3. FDA and USDA intend to clarify and provide guidance on the regulation of cultured animal cell foods.

FDA and USDA staff are in routine contact to ensure that oversight of this food production technology is being implemented consistent with the roles and responsibilities described in the March 2019 Formal Agreement Between FDA and USDA Regarding Oversight of Human Food Produced Using Animal Cell Technology. FDA and USDA staff routinely meet to discuss new information on market and technical developments and considerations related to coordination of field oversight in dual jurisdiction food facilities where animal cell culture occurs.

- a. FDA committed to have premarket consultations with manufacturers of cultured animal cell foods as part of the March 2019 Formal Agreement. FDA intends to issue draft guidance to industry on the consultation process for cultured animal cell foods. This guidance would help manufacturers and other industry stakeholders understand the types of food safety issues they should consider when producing cultured animal cell foods and how to assemble and organize information that can support a firm's conclusion about the safety of their food.
- b. In Calendar Year 2024, USDA will propose new regulations pertaining to the labeling of meat and poultry products comprised of or containing cultured cells derived from animals subject to the Federal Meat Inspection Act or the Poultry Products Inspection Act. USDA will also issue labeling guidance for establishments producing these cell-cultured meat and poultry products.

3. EPA, FDA, and USDA intend to provide updated information on the regulation of modified insect and invertebrate pests and work together to streamline and coordinate the regulation of modified insects.

4. EPA will provide efficacy guidance on genetic modifications in pest animals intended for use as a pesticide.

EPA requires scientific evidence that registered products sold to control pests known to impact public health (such as those that carry West Nile virus, Zika virus, and Dengue) are effective against the target pest. Given the unique parameters involved with field testing of modified mosquito products, EPA will develop efficacy guidance for modified mosquito products for population control.

C. MODIFIED MICROORGANISMS

Stakeholders commented that agency roles and responsibilities remain unclear for various microbial products (e.g., microbial inoculants/biostimulants used for plant growth promotion, plant pests, microbial biocontrol organisms, and microbial biomass used for human and animal feed). The breadth of microbial biotechnology applications continues to grow (e.g., personal care and cosmetic products, chemicals, textiles, water, mining). Stakeholders requested an integrated approach to improving regulatory clarity and harmonization, limiting duplicative oversight, and ensuring risk-proportionate regulation of engineered microbes. Greater agency coordination will minimize the potential for stakeholder confusion or conflicting regulatory requirements among the agencies.

1. EPA and USDA will clarify, and as possible harmonize, regulatory roles, processes, and information, data, and authorization requirements for environmental release of modified microbes.

The agencies will undertake this effort to reduce regulatory duplication where possible, harmonize risk-based processes and requirements, and increase interagency communication, particularly with regard to small-scale field trials. The agencies will:

- a. Identify opportunities for increasing information sharing about specific products, and alignment between application requirements, review processes and timelines, and requirements for small-scale field trials
- b. Identify opportunities to increase harmonization in regulatory exemptions
- c. Explore opportunities for reducing regulatory duplication
- d. Increase interagency communication regarding regulation of modified microorganisms, including by revising and renewing their MOU on modified microorganisms

2. USDA will clarify which modified microorganisms are subject to regulation under its authority.

Under USDA's revised regulations, modified plant pests, microorganisms modified with DNA from a plant pest where the DNA can produce an infectious agent or compound that causes plant disease, and modified microorganisms that are used to control plant pests and could pose a plant pest risk require a permit for import, interstate movement, and environmental release. USDA will:

a. Develop, publish, and maintain a list of plant pests.

In the legacy biotechnology regulations, USDA maintained a regulatory listing of taxa to describe "organisms that are or contain plant pests" to aid developers in determining whether a modified organism required a USDA permit. When USDA updated its regulations in 2020, it removed this listing from the regulations because it had become out-of-date. USDA recognized that taxonomic designations sometimes change, and new plant pests are continually discovered. As such, rather than maintaining a static list of taxa in the regulations, USDA agreed to post a list of taxa on its website that could be regularly reviewed and updated. The availability of this plant pest taxa list plays a key role in providing clarity on USDA regulatory scope and permitting requirements. USDA will partner with subject matter experts to develop, maintain, and update a plant pest list. USDA plans to implement its partnership and begin developing the plant pest list in FY24, and will provide an opportunity for public comment on the list.

3. USDA will explore mechanisms to exempt certain modified microorganisms from its regulation.

As part of the previous activities, and to bring alignment across USDA and minimize duplicative regulation of products that are subject to EPA pesticide regulations, USDA will explore potential regulatory changes that would exempt from USDA regulations, in whole or in part, modified biological control organisms that are not plant pests and are registered with EPA as microbial pesticides or are not EPA registered pesticides but are being transferred, sold, or distributed in accordance with EPA's regulations at [40 CFR 152.30](#).

4. Regulatory pathways to commercialization for non-plant organisms subject to USDA's biotechnology regulations.

USDA will explore potential pathways to commercialization, including mechanisms for risk-based deregulation, for non-plant organisms that could be proposed in future rulemaking, including by considering comments from stakeholders on the Request for Information issued in November

2022, further engaging impacted developers and other stakeholders, and consulting with EPA and FDA.

5. USDA will streamline its permitting process and update its user guides.

In order to improve the efficiency and predictability of our permitting process for modified microbes, in April 2024, USDA standardized supplemental permit conditions for import and interstate movement permits for modified microbes, enabling permits of up to three years duration, multiple species within a genus of bacteria and fungi under a single permit, and multiple origin and destination locations on import permits. USDA also released a voluntary [Standard Operating Procedure template](#) to assist applicants with completing permit applications for movements and releases of modified microbes. In addition to these actions and the actions noted above to streamline the permitting process for modified plants, beginning in FY24, USDA will:

- a. Further streamline permit application and review processes** to enable efficient movement of modified microbes between APHIS-approved containment facilities for contained research activities.
- b. Streamline Supplemental Permit Conditions** for microbe release permits to ensure USDA assigns permit conditions that meet USDA protection goals, are consistent among developers, and provide concise, plain-language requirements.
- c. USDA will further revise its draft microorganism permit guide.**

In October 2023, USDA published a revised draft guide for submitting permit applications for modified microorganisms and a response to public comments on the initial draft guide issued in March 2023. The revised draft guide included information requirements for determining regulatory jurisdiction for microorganisms. As part of its ongoing commitment to further clarify the guide, after intra- and interagency consultation USDA will publish a further revision of the draft guide and make it available for public comment, including providing information on USDA processes, criteria, and any associated data requirements for determining regulatory jurisdiction for microorganisms based on whether an organism is a plant pest or biocontrol organism that could pose a plant pest risk. This guide will harmonize, as possible, information and data requirements for modified and non-modified microbes subject to USDA regulation under the Plant Protection Act.

6. EPA biopesticide technical assistance and application review prioritization.

Biopesticides often have lower toxicity profiles, reduced worker re-entry intervals and reduced pre-harvest intervals. They can also support climate change mitigation (e.g., by providing alternatives to ozone depleting pesticides or reducing on field applications and use of fossil fuels) and help advance environmental justice. In light of these benefits, EPA will prioritize review of biopesticide applications, provide technical assistance to biopesticide developers and seek to collaborate with state lead pesticide agencies in order to reduce the time to bring new and effective biopesticide tools to farmers, as resources allow and in alignment with the Pesticide Registration Improvement Act (PRIA 5).

D. HUMAN DRUGS, BIOLOGICS, AND MEDICAL DEVICES

Stakeholders commented that FDA should update or issue new guidances or regulations in a variety of areas related to human drugs and biologics, such as aseptic processing of sterile drug products, validation and testing procedures, quality metrics reporting, the manufacture of multiple products

in a single facility, lot release and product characterization requirements, cross-referencing of drug master files, sterility assurance and contamination control, and certain animal testing requirements. A commenter requested that FDA rather than EPA oversee products with anti-biofilm claims. Another commenter recommended that the United States should foster the domestic manufacture of active pharmaceutical ingredients.

1. FDA intends to issue a proposed rule to revise regulations related to post-approval chemistry, manufacturing, and controls (CMC) changes for both drugs and biological products, and intends to issue draft guidance to provide greater clarity on its oversight of post-approval CMC changes for certain biotechnology products.

- a. FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) are developing a proposed rule to revise regulations related to post-approval CMC changes (21 CFR 314.70, 314.81, 601.12) to facilitate further application of risk-based approaches, including the use of tools described in the internationally harmonized guidance ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management. The proposed revisions are intended to allow for a more risk-based approach to regulation of changes sponsors make to approved products and will apply to every biotechnology product seeking to make post-approval CMC changes. They also will better harmonize with approaches taken internationally with respect both to launch activities and to post-approval changes.
- b. In July 2023, CBER issued the draft guidance [Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products](#) (CGT products) to provide more guidance on post-approval changes in these products. The draft guidance references and aligns with the existing more-general guidance on post-approval changes for drugs and biological products, but also identifies and provides recommendations for challenges specifically presented by CGT products that are not addressed by existing guidance. Industry has sought clarity on the topic (e.g., how are such changes qualified, does there need to be a comparison to the reference product).
- c. CDER and CBER are also developing a draft guidance on post-approval manufacturing changes to biosimilar and interchangeable biosimilar products to provide clarity on how to make post-approval changes for biosimilar products.

2. FDA is developing guidance on its oversight of certain genome-editing products, including use of a platform approach to such therapeutics.

- a. In January 2024, CBER finalized the guidance [Human Gene Therapy Products Incorporating Human Genome Editing](#). This guidance addresses development of human genome editing products for clinical studies and licensure. Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. FDA generally considers human gene therapy products to include all products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include nucleic acids, genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and ex vivo genetically modified human cells. Over the past 10 years, the level of interest in human genome editing as a scientific technology used in the treatment of human disease has increased substantially, and there has been rapid

development of gene therapy products incorporating genome editing. Many platforms exist to design genome editing components, particularly the targeting elements. Some of the specific risks associated with genome editing approaches include off-target editing, unintended consequences of on- and off-target editing, and the unknown long-term effects of on- and off-target editing. While the potential of such products for the treatment of human disease is clear, the potential risks are not as well understood. To assist in the translation of these products from the bench to clinical trials, this guidance includes recommendations for how to assess the safety and quality of these products and address the potential risks of these products. As the field evolves, product design advances, and FDA gains information on the safety of human genome edited products, FDA may revise its recommendations to take into account such changes.

- b. CDER and CBER also plan to issue draft guidance to implement section 2503 of the 2023 Consolidated Appropriations Act. To implement this provision, FDA intends to establish a platform technology designation program. The guidance would describe the program and how interested persons can submit a request for a platform technology to be designated. If a platform technology designation request is granted, FDA may accept a request for expedited development for any subsequent application submitted under sections 505(b) of the Federal Food, Drug, and Cosmetic Act or 351(a) of the Public Health Service (PHS) Act that uses the platform technology. Expedited development for a subsequent application may include engaging in early interactions with sponsors to discuss the use of a platform technology and providing timely advice to and having additional engagement with the sponsor during the development program.
3. **In January 2024, FDA-CBER finalized the guidance [Considerations for the Development of Chimeric Antigen Receptor \(CAR\) T Cell Products](#).** The guidance provides CAR T cell-specific recommendations regarding CMC, pharmacology and toxicology, and design of clinical studies for cancer indications. This guidance also provides recommendations for analytical comparability studies for CAR T cell products. The guidance will help facilitate development of these critically important new products, including by developers in other countries who want to know FDA's recommendations on their manufacture and clinical evaluation. The guidance is based on regulatory expectations that the FDA has used historically, including for the development and approval of the currently licensed six CAR T cell products, and aligns with global regulatory standards.
 4. **In December 2023, FDA-CBER updated the guidance [Potency Assurance for Cellular and Gene Therapy Products \(CGT products\)](#).** This revised draft guidance document updates the agency's recommendations for potency assays for CGT products and further recommends a comprehensive approach to ensuring potency that is grounded in quality risk management. Potency assays remain an important part of ensuring potency, but the comprehensive framework in this guidance document also includes complementary approaches to help ensure the potency of CGT products.
 5. **FDA will continue to partner, along with the National Institutes of Health and multiple public and private organizations, in the Accelerating Medicines Partnership Bespoke Gene Therapy Consortium Public Private Partnership.** The Partnership informs regulatory decision-making and regulatory policy development. It aims to develop platforms and standards that will speed the development and delivery of customized or 'bespoke' gene therapies that could treat the millions of people affected by rare diseases. The

effort aims to overcome major obstacles related to developing gene therapies and will create a gene therapy protocol book that the research community can use to make the process of developing gene therapies for rare conditions much more efficient.

E. CROSS-CUTTING ISSUES

1. Regulatory clarity and assistance to developers

Commenters had many requests and suggestions for greater clarity on and assistance with the regulation of biotechnology products that fall under the Coordinated Framework. In addition to requests for increased clarity in specific product areas, as discussed above, commenters asked the regulatory agencies to provide simple, plain language information that clarifies agency responsibilities for different products, data requirements and regulatory processes, and the bases for decision-making. Commenters suggested using the Unified Website for Biotechnology Regulation to provide plain language summaries of regulations as well as guidance and documents such as case studies, and as a one-stop shop for stakeholder questions and updates. Commenters asked the agencies to provide dedicated staff who would be directly available to provide regulatory assistance to developers. In addition to actions described above to increase regulatory clarity and assistance, EPA, FDA, and USDA will:

a. Work together to provide plain language information on regulatory roles, responsibilities, and processes for products of biotechnology.

1. In November 2023, the agencies released [plain-language information](#) on the regulatory roles and responsibilities of each agency on the Unified Website for Biotechnology Regulation, appropriately updated to reflect regulatory developments since 2017, including case studies that show how several example products would be regulated. The agencies will continue to update this information and further clarify the Coordinated Framework as other work items in this Plan come to completion.
2. EPA, FDA, and USDA will undertake a pilot project to explore and consider the feasibility and costs of developing a web-based tool for guiding developers to appropriate information about which regulatory agencies may regulate a given product category.

b. Develop and implement a mechanism for developers to submit information to, and request a meeting with, all three regulatory agencies, early in the product development process.

The agencies will modify the “Contact Us” page on the Unified Website for Biotechnology to enable developers to voluntarily provide the agencies with a set of basic, non-confidential information and request a virtual meeting to discuss the regulatory path forward for their product. The principal purpose of such meetings would be to clarify jurisdictional questions about regulatory oversight of the product and provide initial regulatory guidance. In general, when, based on the provided information, the three agencies agree that a product would be regulated by only one of the agencies (for example, a human medical product regulated solely by FDA), the agencies would identify for the developer the agency with which it should conduct further correspondence to obtain regulatory advice through that agency’s usual procedures. For products that would be regulated by more than one agency or for which the appropriate regulatory agency is unclear, the agencies would arrange a meeting to clarify jurisdictional questions about regulatory oversight of the product, provide

preliminary regulatory guidance, and explain the process for obtaining regulatory advice from the relevant agencies thereafter.

2. Interagency Coordination and Harmonization

Commenters stressed the need for greater policy and process alignment across EPA, FDA, and USDA regarding regulation of biotechnology products to reduce uncertainties for developers and avoid unnecessary redundancies. Commenters urged the agencies to align definitions, regulatory exemptions, data and other information requirements, and timelines for reviews, to coordinate reviews and recognize their sister agencies' expertise, and to establish a single point of entry into the regulatory system. Further, they asked for coordination across all federal agencies that touch products of biotechnology, from regulatory and trade agencies to administrative and security agencies and made various recommendations for establishing a formal interagency coordinating body. In addition to working together on some of the actions listed above, EPA, FDA and USDA intend to:

a. Update and renew their information sharing MOU.

To improve and broaden communication and coordination between the regulatory agencies, EPA, FDA, and USDA intend to update their existing information sharing MOU to add regulatory programs not currently included in the MOU. As part of this effort, the agencies intend to also pursue mechanisms for and modify the MOU to better enable the sharing of protected information, in a manner that is consistent with legal requirements, when approached by developers with unique products where product jurisdiction may not immediately be clear or where there is overlapping jurisdiction. An updated MOU will better enable the agencies to communicate and coordinate on products for which key information is protected from disclosure and will facilitate greater coordination on streamlining biotechnology regulations while ensuring they remain comprehensive in scope.

b. Work together to update the Coordinated Framework for the Regulation of Biotechnology by December 2024.

The Coordinated Framework was last updated in 2017 and included a history of U.S. policy for regulation of biotechnology products, detailed information about roles and responsibilities of the primary agencies that regulate biotechnology products, and case studies that described how several example products would be regulated. The agencies intend to update the Coordinated Framework to reflect regulatory changes and to provide additional clarity. As part of this work, the agencies intend to work to streamline and harmonize the Coordinated Framework where possible and intend to review the Coordinated Framework on a biannual basis to ensure it remains up to date as science and technology advance. Additionally, by December 2024, the agencies intend to post brief, plain language summaries of the regulatory roles and processes for specific product use categories on the Unified Website, to further aid developers in identifying which agencies would regulate their products.