Report on Stakeholder Outreach Related to Ambiguities, Gaps, Uncertainties in Regulation of Biotechnology Under the Coordinated Framework

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

Regulation to Support Safe Innovation

In an effort to further regulation that supports safe innovation, the US Department of Agriculture, the Environmental Protection Agency, and the Food and Drug administration undertook efforts to identify and clarify areas of uncertainty in the Coordinated Framework for the Regulation of Biotechnology, and to identify areas where efficiency in regulatory processes could be improved. The three agencies began the process with a Request for Information (RFI) to the public, open from December 15, 2022, through February 3, 2023. Specifically, the RFI asked all interested parties to respond to seven key questions:

1. Describe any ambiguities, gaps, inefficiencies, or uncertainties regarding statutory authorities and/or agency roles, responsibilities, or processes for different biotechnology product types, particularly for product types within the responsibility of multiple agencies.
    a. Describe the impact, including economic impact, of these ambiguities, gaps, inefficiencies, or uncertainties.
2. Provide any relevant data or information, including case studies, that could inform improvement in the clarity or efficiency (including the predictability, transparency, and coordination) of the regulatory system and processes for biotechnology products.
3. Describe any specific topics the agencies should address in plain language on the regulatory roles, responsibilities, and processes of the agencies.
4. Describe any specific issues the agencies should consider in developing a plan to implement regulatory reform, including any updated or new regulations or guidance documents.
5. Describe any new or emerging biotechnology products (e.g., microbial amendments to promote plant growth; food plants expressing non-food substances or allergens from non-plant sources) that, based on lessons learned from past experiences or other information, the agencies should pay particular attention to in their evaluation of ambiguities, gaps, or uncertainties regarding statutory authorities and/or agency roles or processes.
6. Describe any new or emerging categories of biotechnology products on the horizon that the regulatory system and processes for biotechnology products should be preparing to address. Describe any specific recommendations for regulating these new or emerging categories of biotechnology products to guide agency preparations.
7. What is the highest priority issue for the agencies to address in the short term (i.e., within the next year) and in the long term?

Feedback

To gain insight into the questions outlined in the RFI, the agencies solicited written and oral comments from stakeholders. During the open comment period, the agencies received a total of 88 distinct public comments via Regulations.gov, many of which provided responses to several of the questions asked. Members of the developer community submitted a majority of the comments, including developer organizations of all sizes, academic researchers, and persons from outside of the United States. Stakeholders with an interest in biotechnology regulation also submitted comments to the agencies, including producer, manufacturer, and retailer groups as well as several public interest non-governmental organizations, one of which submitted a sign-on letter from 6,083 members.

The three regulatory agencies organized a virtual listening session on January 12, 2023, open to anyone interested in offering feedback and/or listening to feedback from others. The 450 registrants for this

listening session included developers, lobbyists, legal representatives, industry groups, non-governmental organizations, and other government entities. They included individuals from 19 countries, with both government and industry participants. Of the 450 registrants, 34 expressed interest in offering comments. Ultimately, 281 registrants attended part or all of the listening session, and 16 offered comments.

In addition, representatives from the U.S. Government were invited to and attended the following listening sessions organized by stakeholders.

Date	Organizer	Number of commenters
January 28, 2023	American Seed Trade Association	11
January 31, 2023	Biological Products Industry Alliance	7
January 26, 2023	Biotechnology Innovation Organization	18

Comments and Themes

In reviewing the comments on the RFI, several themes emerge: 1) requests for greater Regulatory Clarity, 2) requests for greater Regulatory Coordination and Harmonization, 3) requests for Regulatory Reform or Revision, and 4) comments on Regulatory Resources. In some cases, there is overlap among these themes. Many commenters provided input into more than a single area. We summarize the comments representing each area below.

Regulatory Clarity

As requested under the RFI, commenters provided input on the need for regulatory clarity on various aspects of regulation across the three agencies. Some commenters asked that regulatory agencies provide simple, plain language information that clarifies which agency or agencies have responsibility over different products and why, the scope of regulations, data requirements, regulatory processes, and the bases for decision-making. As one commenter wrote, "It would be helpful if different agencies could coordinate a unified public message that clearly delineates which agencies are responsible for regulating different types of bioengineered organisms and products."

Commenters also requested clarity about several specific categories of products, including microorganisms, gene-edited organisms, cultured animal cell foods (also referred to as cell-cultured or cell-cultivated meat or poultry food products), and plants. Many commenters requested clarity around the regulation of genetically modified microorganisms. The primary concern was clarification regarding each agency's role and responsibility depending on the microorganism and its use, particularly microbial biomass used for human and animal feed, microbial inoculants/biostimulants used for plant growth promotion, plant pests, and microbial biocontrol organisms.

Commenters also sought clarity on the regulation of genome-edited organisms at each agency, including improved guidance on when an organism would be regulated. For example, commenters requested clarification of FDA's and USDA's roles in the regulation of genome-edited food animals, and greater clarity from EPA and FDA regarding their approach to regulation of genome-edited plants. A commenter also stressed the need for USDA to have a more transparent method of determining if a gene-edited

product requires a Bioengineered label, noting the current practice of making this determination after commercialization is too late in the development process.

Another area where commenters requested clarity was on the regulation of cultured animal cell foods. Commenters requested that FDA and USDA share additional guidance on the evaluation process, review timelines, and the information needed to demonstrate food safety.

Commenters also sought additional information on USDA-APHIS' Regulatory Status Review process for modified plants to better understand how APHIS identifies and assesses plausible plant pest risks, including access to underlying documents and information about potential data requirements when a plausible risk is identified.

Finally, many commenters referred to the Unified Website for Biotechnology as an important mechanism for improving clarity and offered many suggestions for enhancements, including: leveraging it as a one-stop shop for stakeholder questions and stakeholder updates, including notices on rulemaking and listening sessions and a joint listserv for receiving updates; using it to provide plain language summaries of regulations and guidance and documents such as case studies on the regulation of various biotechnology products, as well as to provide updates to guidance documents with changes highlighted; using it to rectify misconceptions (e.g., that CRISPR-edited crops are not regulated); and posting organizational charts and appropriate contact information. Finally, some commenters suggested that the Unified Website house an automated algorithmic tool or a regulatory decision-tree or chatbot-style system that developers could use to determine the appropriate agencies and points of contact they should contact for answers about their product and to initiate regulatory reviews.

Regulatory Coordination and Harmonization

Many commenters provided input on regulatory coordination and harmonization.

Commenters provided several suggestions on how to promote coordination and harmonization across *all* federal agencies that touch products of biotechnology, from regulatory agencies, to trade agencies, to administrative and security agencies. Some suggested that the Office of Science and Technology Policy (OSTP) and other EOP agencies are best positioned to establish overarching bioeconomy regulatory policy and to resolve interagency regulatory differences; others suggested establishing an agriculture biotechnology interagency working group, coordinated and co-chaired by OSTP, the Office of Management and Budget, the Office of the U.S. Trade Representative, and the National Security Council, or some other coordinating body to facilitate interagency coordination and cooperation. Finally, several commenters advocated for the formation of a Bioeconomy Initiative Coordination Office (ICO). Although the functions of the ICO would be much broader than biotechnology regulation, it would, in part, be a focal point for interagency collaboration in coordinating the regulatory system, and would link regulators with industry, academia, and others, and engage in horizon scanning activities. Whichever approach is adopted, commenters suggested that implementation of commitments resulting from Section 8 should be monitored to ensure accountability, and that a sustainable mechanism to periodically assess the impact of regulations should be adopted.

Regardless of how coordination is achieved, commenters stressed the need for greater policy and process alignment across USDA, EPA, and FDA regarding regulation of biotechnology products to reduce uncertainties for developers and avoid unnecessary redundancies. Commenters urged the agencies to align definitions, regulatory exemptions for genome-edited plants, data and other information

requirements, and timelines for reviews, and to recognize their sister agencies' expertise, so as to promote predictability, reduce redundancy, and enable synchronous agency decisions that support trade. Many commenters suggested a coordinated process among agencies for providing regulatory guidance to developers, and some suggested a single point of entry to the regulatory system. This single point of entry (which they suggested should be staffed from regulatory, research, and other relevant agencies familiar with policy, legal interpretation, and technical review of submissions to agencies) would determine which regulatory body will have precedence for the oversight of a product and its intended use and would arrange direct contact with the relevant agencies in a timely manner. One commenter suggested that such a process could result in a unified submission process through which FDA, EPA, and USDA coordinate product reviews and assign agency jurisdiction.

A commenter also suggested that an interagency working group should collect data on how previous products have passed through the regulatory process to supplement case studies developed in the 2017 update to the Coordinated Framework, inform the development of a single point of entry concept, and identify bottlenecks and areas of dual review. In the context of synchronizing reviews, one commenter stated that there should be improved coordination between EPA and USDA on the regulation of herbicides and herbicide resistant plants such that a company developing the herbicide tolerant variety should not be allowed to commercialize the new variety until after the EPA has registered a product for the herbicide tolerant crop. More generally, a commenter stated that expertise could and should be shared among agencies while maintaining the primary responsibility of the agency for a regulated product. Lastly, whether conducted by OSTP, the regulatory agencies, and/or contractors, some commenters saw the need for a formal horizon scanning mechanism for new developments in products arising from the application of emerging biotechnologies to proactively inform updates to regulatory processes. However, others felt that formal horizon scanning would not be good use of limited regulatory resources, particularly as many products destined for commercial release in the next 10 years are already possible to anticipate without horizon scanning, and that the focus should instead be on quickly tackling existing issues.

Many commenters requested improved cooperation and a harmonized approach across the agencies in the handling of microbes since they are often regulated by more than one agency under the Coordinated Framework. Commenters offered many suggestions for improving harmonization and limiting duplicative oversight, such as: common language and harmonized definitions; a harmonized approach to determining which engineered microbes require oversight and to exemptions from regulation; aligning requirements for small-scale field testing across agencies; establishing cross-representative Centers of Excellence to review certain types of products or delineating a lead agency to review particular products based on expertise; sharing safety data and knowledge across agencies; and establishing harmonized review processes that evaluate the risk of modified microbes relative to their wild-types.

Lastly, commenters also pointed out that intra (and not just inter) agency coordination is necessary to promote regulatory efficiency. For example, a commenter noted the importance of USDA Biotechnology Regulatory Services and Plant Protection and Quarantine closely coordinating to delineate each program's jurisdiction, avoid regulatory duplication, and ensure alignment in categorizing microorganisms. Another commenter noted that with respect to FDA, biotechnology product reviews for food and feed uses are distinct, with each program maintaining its own review process and priorities. In

short, commenters believed biotechnology products should be evaluated consistently across and within agencies using transparency of review process with clear review timelines that avoid duplication.

Regulatory Reform or Revision

Comments in this area provided a variety of different concerns specific to each agency as well as concerns common to all agencies, including the need for streamlining regulatory processes and reducing potentially duplicative regulation. Some commenters pointed to the need to fill gaps that exist for certain products, while others suggested that agencies are over-extending their authorities or their scope. Some comments suggested that agencies need to consider labelling issues for certain products.

With respect to regulatory reform, a group of commenters urged more thorough and continuing oversight for products of biotechnology, while the majority of individual commenters indicated regulations should be less complex and only apply when a product creates a new or different risk than one that was previously reviewed. Commenters in the majority group indicated the regulatory frameworks should be updated to account for advances in technology (like genome editing) and constructed to rapidly adapt to future innovations in science and technology, and believed these changes, coupled with improving the speed and communication of responses from the regulatory agencies, would help broaden the use of innovative crop improvement techniques by institutions and businesses of all sizes. These commenters also provided comments specific to each agency, which are described further below.

Commenters who called for strengthening regulatory oversight for agricultural products of biotechnology offered a number of suggestions for bolstering current regulations in the short-term, while suggesting that in the long-term Congress should establish statutory authorities that enable regulatory agencies to conduct science-based risk assessment of biotechnology products without regard to the objectives of agency marketing and trade programs. A large group of commenters collaborated on a single opinion that encourages "action towards implementing proper regulations and oversight for genetically modified organisms (GMOs) and other biotechnology products," noting failure "to develop specific regulations to assess the human and environmental health effects of biotechnologies." Commenters within this group also suggested updates to the Coordinated Framework to integrate the Biden Administration "Framework for Federal Scientific Integrity Policy and Practice" and to specify how human, animal and environmental health and biodiversity are to be protected. They requested that agencies regulate based on the whole lifecycle of a process of production rather than on the final product and adopt the OSTP definition of biotechnology products in their regulations ("products developed through genetic engineering or the targeted or in vitro manipulation of genetic engineering of organisms, including plants, animals, and microbes"). Commenters also pointed out concerns with transparency in granting Confidential Business Information status to developer data, encouraged establishing a requirement for submission of complete genomic sequences of the modified plants, animals and microbes and clear label information, and advocated for a federally-operated national registry of gene-edited plants so that consumers can make informed choices about products using new or emerging biotechnology and other producers can manage co-existence. They opposed regulatory definitions and evaluation methods that assume an equivalence between conventional or wildtypes and genetically engineered (GE) products, especially for gene drives; indicated developers should be prevented from making claims about the product benefits prior to pre-market safety reviews, post-market safety reviews and review of field trial data by agency scientists; called for a moratorium on commercial and environmental releases of gene drives and establishment of regulatory guidelines that

align with the UN Convention on Biodiversity; and urged USDA to add noxious weed provisions to its biotechnology regulations to regulate direct and indirect harms from GE crop production systems such as contamination from transgenic seeds, herbicide resistant weeds, public health impacts, and economic harm to farmers.

Commenters who believed biotechnology regulations should be streamlined and less complex offered suggestions on improving and reducing costs associated with USDA's permitting process for modified plants and organisms for field trials. Commenters encouraged USDA to restore the notification process that allowed for streamlined authorizations for certain types of field trials, streamline procedures and information requirements for interstate movement permits (especially when moving an organism from one contained facility to another), improve guidance for developers applying for permits to release modified microorganisms into the environment, ensure permitting conditions are consistent with agricultural practices, and improve the efficiency of its online permitting portal. Commenters also urged USDA to broaden regulatory exemptions to account for natural variation that exists in plants or mirror what can be accomplished through conventional breeding, including multiplex editing and edits made across multiple homologous chromosomes in polyploid species. In that regard, commenters suggested that, to speed and facilitate science-based exemptions in the near-term, USDA should convene a panel of experts in the fields of breeding, mutational breeding, molecular genetics and agronomy to provide a clearer understanding of the variation that is practically achieved and used to develop new plant varieties. Commenters also encouraged USDA to adopt exemptions for modified microorganisms, such as modifications for the purpose of DNA barcoding used solely for research purposes. Commenters noted that, although USDA exempts previously reviewed plant–trait–mechanism of action (MOA) combinations from future regulation, such exemption has limited effect when other federal agencies continue to re-review the same products and emphasized the importance of harmonization of roles among the agencies on this matter, as well as on exemptions for genome-edited products.

With respect to USDA's Regulatory Status Review (RSR) process, commenters acknowledged USDA's updated regulatory framework geared toward science-based, risk-proportionate oversight, while noting a critical need for the Agency to hit regulatory performance targets and provide greater clarity about data requirements to achieve a truly predicable process for making business decisions. Commenters also encouraged USDA to allow public and private plant breeders to support development of Plant Reference Documents, to defer to EPA's analysis of potential impacts to Non-Target Organisms that are unrelated to actual plant pest harm as defined in the Plant Protection Act. Lastly, commenters stressed the need for an RSR-like process for microorganisms developed through genetic engineering to enable commercialization of such products.

With respect to FDA, commenters' feedback focused on two primary areas: review of foods derived from new plant varieties, and oversight of GE animals. However, a few commenters addressed oversight of human drugs and biologics and a few others discussed oversight of products added to animal feed.

With respect to foods derived from new plant varieties developed through genome editing, commenters stated that FDA should issue draft guidance that reassert the applicability of its 1992 Statement of Policy for Foods Derived from New Plant Varieties including plants with added substances; that orally consumed DNA, RNA and most proteins are generally recognized as safe; and that plants with no added substances are not regulated under FFDCA Section 409. Commenters also encouraged FDA to streamline review processes for familiar products, rather than continuing product-by-product review. A few

commenters found a lack of clarity regarding FDA's role in reviewing products that may introduce allergens into commodity crops, with one identifying this as a significant gap in the Coordinated Framework, while others asserted oversight responsibilities for such products "are extensive, clear, and well understood, and provide more than adequate authority to ensure" their safety and stated that FDA and USDA should work with crop developers and other stakeholders to develop and adopt science- and risk-based standards for food crop segregation, grain management, and other controls to mitigate risks relating to the production of biotech food crops produced to contain allergenic proteins.

With respect to GE animals, some commenters stated that FDA's use of drug approval authorities results in FDA requirements going beyond requirements needed to address unreasonable risks associated with GE animals. Another commenter did not believe FDA's drug authority was adequate to review GE animals and advocated for mandatory evaluations based on a precautionary risk and hazard assessments. Some commenters stressed the importance of providing clarity about the regulatory process, noted the ongoing discussions between HHS and USDA related to the oversight of modified food animals, 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. One commenter indicated that animals modified for disease resistance should not be permitted to enter commercial populations and the food chain.

With respect to human drugs and biologics, commenters recommended that FDA update or issue new guidance or regulation in a variety of areas 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.

With respect to animal feed, a few commenters requested that FDA update its policies regarding labeling and oversight of products intended to provide environmental, production, food safety or animal health benefits when added to animal feed.

With respect to EPA, several commenters indicated that EPA should confirm its regulatory focus on pesticidal substances intended to prevent, destroy, repel, or mitigate a pest through a specific toxic mode of action that acts directly on a pest and should not designate as plant-incorporated protectants (PIPs) genetic modifications that result in characteristics related to growth, development, structure, yield, stress tolerance, etc., of the plant, and that have a non-toxic mode of action (e.g., resistance proteins, transcription factors, others). Commenters also urged EPA to proceed with issuing its rule to exempt certain PIPs, while noting concerns with EPA's original proposal, such as narrow exemption criteria and a burdensome process to qualify for exemption from regulation. One commenter said EPA should require full environmental impact reviews for novel applications and genetically engineered insects.

Some comments address issues affecting multiple agencies. With respect to microorganisms, one commenter suggested that it is difficult to assess the consequences of microbe releases, which may prevent regulators from quickly approving potential applications, and thus modified microbes should be tested in microcosms that closely mimic real environments before performing field tests. Another

commenter suggested situations where a "fast-track" approval process may be warranted, for instance, when a modified strain is largely identical to an approved strain with only minimal changes that do not affect risk.

With respect to product labeling, one commenter recommended that regulations and guidance documents should prevent the use of terminology such as "vegetarian," "vegan," "animal-free," or "plant-based" on product labels of products produced through genetic engineering based on the DNA of animals (whether based on actual DNA, cell lines, or virtual DNA). The commenter stated that such labels would be confusing and misleading for consumers who, for religious, ethical, philosophical, environmental, or other reasons do not want to purchase products in which animal products were used at some point in production.

Finally, one commenter encouraged agencies to consider approaches like FDA's Fast Track and Breakthrough designations, which prioritizes innovations that meet unmet needs or represent a significant improvement over current leading products, noting this approach incentivizes companies of all sizes to work on underserved markets.

Regulatory Resources

This category includes general comments on the need for increased resources for regulation. Multiple commenters expressed concern that the regulatory agencies were under-resourced and that this is harming the commercialization of innovative new products. Commenters stated that regulatory agencies need to be funded and staffed appropriately, with additional staff training, to address some of the issues around "timely" and "consistent" reviews. Commenters observed that additional resources are needed at each agency to ensure capacity to review new products in a timely manner, with some noting that EPA and FDA may be particularly underfunded. For example, one commenter wrote that "to achieve the progress described in the Executive Order, agencies should be staffed, trained, and resourced in a manner that reflects the changing bioeconomy and the urgency of the opportunity," while another wrote "we respectfully request that OSTP do everything it can to ensure that agencies have all the resources – including personnel and scientific expertise – they need to conduct efficient regulatory reviews and adhere to predictable regulatory timelines." Some commenters also suggested that additional training should be provided to regulatory staff to help them stay current with innovation in research and technology.

As noted above, there was a specific suggestion for establishing an ICO, including dedicated funding for staff. According to the commenter, the ICO would undertake two activities relevant to regulatory resources. First, it would perform horizon scanning for emerging technologies and innovations to ensure regulatory agencies are prepared to address emerging technologies (although as noted above, other commenters felt this was a poor use of resources). Second, it would establish an interdisciplinary Training Fellowship of one-or two-year duration, "which includes cross-training in the interdisciplinary skills needed to evolve effective regulatory mechanisms for the emerging products of biotechnology." Some commenters focused the Fellowship primarily on regulators, while others stated that it should be available to individuals both within and outside of the regulatory agencies and could "build a strong national cohort of talent" that "could be redeployed to the government or bring first-hand knowledge of the system to stakeholders such as product developers, funders, and academic researchers."

Finally, some commenters requested additional resources to assist researchers and product developers. In particular, vis-à-vis the suggestions for a single point of entry into the regulatory system, commenters

recommended dedicated staffing from the regulatory agencies, including a designated case manager who could direct inquiries and facilitate interactions with inquirers, but noted that implementing a single point of entry into the system would further stress the regulatory system if implemented as an unfunded mandate. Commenters also suggested that the agencies designate regulatory scientists who would serve as affiliates to biomanufacturers and "could be directly available to assist developers in the regulatory process."

Miscellaneous

Several commenters also recommended addressing gaps in biotechnology education, requested greater oversight of laboratory research on novel pathogens, expressed concern about the safety of food produced through genetic engineering, and requested that FDA coordinate with the Tax and Trade Bureau on oversight of microbes used in winemaking, that FDA modify its delineation between drugs and dietary supplements, that FDA and EPA revisit their policies regarding which agency oversees GE microbes used in the manufacture of components of cosmetics and of detergents used to clean re-usable medical devices, and that there should be heightened efforts at international coordination of regulatory policy and approvals. Other commenters requested clarification of the regulatory status of "plant biostimulants." Comments generally requested that biostimulants be excluded from FIFRA regulation. One commenter indicated there was no demonstrated need for regulation of GE organisms. One commenter asked for regulatory definitions of "biobased" and "natural" that could be verified through laboratory testing under the ASTM D6866 standard using a lab accredited at ISO/IEC 17025:2017 or higher.

Although most of the comments submitted in response to the RFI were critical of the current state of regulation under the Coordinated Framework and/or offered suggestions for improvement, supportive comments were also offered. For example, several commenters felt that the Coordinated Framework is without gaps, is clear and well understood, and is sufficiently comprehensive to allow for safe commercialization of products. One commenter, whose current products are subject only to regulation by FDA and USDA, stated "Both FDA and USDA APHIS are doing things that are very positive and should be encouraged. One of these strengths is the quality of the scientific reviewers and the fact that the agencies encourage informal pre-submission discussions and consultations with researchers and developers." Although there were many criticisms of USDA's revised biotechnology regulation, commenters nonetheless recognized them as, "a major advance" that was "a positive step towards risk proportionate regulations" for which "USDA APHIS needs to be commended." One commenter stated that "Historically, USDA has had an excellent track record regulating plant biotechnology based on science and risk." The commenter was also broadly supportive of the objectives of the proposed revisions to EPA regulations, stating "we believe that the rationale behind the proposal is well-justified scientifically, will not result in any novel risks to the environment or to human health, and has the potential to facilitate the development of innovative applications of cutting-edge genetic tools in a wide variety of crops and economically important plant species." This commenter also noted that "The U.S. has led the way in developing [innovative biotechnology products] due to thoughtful, bipartisan public policy. This has created a favorable climate in which to undertake the lengthy and risky job of investing in and developing the next biotech breakthroughs; allowing producers to use new technologies; and ensuring a pathway to market for new products." Finally, a commenter noted that the Unified Website for Biotechnology Regulation "is a useful resource for the public to access information on agencies

regulatory authorities and roles" and that "industry appreciates the ability to readily contact agencies through the website."