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SUBJECT: **Request for Information:**
Exploring Pathways to Commercialization for Modified Microbes
Docket ID APHIS-2024-0002
Submission of Comments

Dear Mrs. Huff-Woodard:

Thank you for the opportunity to comment on the subject *Federal Register* **Request for Information (RFI)** concerning USDA-APHIS-BRS's **Exploring Pathways to Commercialization for Modified Microbes**. The Biological Products Industry Alliance (BPIA) submits herewith these comments.

By way of introduction, BPIA promotes the responsible development of safe and effective biological products, including biopesticides, biofertilizers, and biostimulants. These beneficial tools are used in various settings, including commercial agriculture, forestry, golf courses, home gardens, horticulture, and ornamentals. BPIA also supports public health through education, outreach, and advocacy activities at the state, federal, and international levels. BPIA's membership includes large and small producers of biological products used extensively by US farmers, including organic growers and producers of pesticide inert ingredients.

DISCUSSION

We at BPIA are grateful for the chance to provide input on this RFI for developing more streamlined processes to enable the commercialization of modified microbial products produced through biotechnology including new technologies. We are committed to leveraging scientific understanding to underscore the importance, usefulness, and advantages of biological products in agriculture and the environment at large.

RFI QUESTIONS AND BPIA RESPONSES

BPIA's responses to the questions outlined in the RFI as presented below.

Question 1: Describe new or emerging categories of biotechnology products that are relevant to the development and use of modified microorganisms. To assess new and emerging technologies with modified microbes, what expertise and resources are needed in the government to evaluate the overall plant pest risk of modified microbes?

BPIA RESPONSE: Products of biotechnology are used or envisioned in myriad applications, including pharmaceuticals and agricultural input materials. The capabilities of product ideas are endless. When considering agricultural products, many existing "biologicals" — biopesticides, biocontrols, biofertilizers, and biostimulants — can be enhanced with or derived from modified microbes or their metabolites. Moreover, nanotechnology is being increasingly used to deliver pesticidal active ingredients (AIs), including microbials. Whole genome sequencing and multinomics approaches are rapidly being developed to inform soil-microbe-plant interactions and "mode of action" information.

While the potential for products and methods of production are seemingly limitless, the focus for regulatory purpose should be on the end product. The evaluation conducted under the biotechnology framework should be product-dependent not process-focused. Common technologies used to modify microorganisms can include but are not limited to CRISPR/Cas9, random mutagenesis, and base editing; however, the regulations should be agnostic as to

how a product is developed, but rather focus on the composition and potential risk of the final product. In doing so, the evaluation process will remain valid irrespective of what technologies are developed in the future by evaluating the resultant final product and whether, in its final form, the product has increased plant pest potential. If not, BRS should be exempting it from permit requirements as the scope would be outside of the 7 CFR Part 340 mandates.

Many companies are interested in standard testing approaches designed specifically for modified microorganisms, not simply adjusted from previous approaches, such as for modified plants or for chemical ingredients. Additionally, a suggestion would be for BRS to acquire additional expertise on microbe life cycles and soil sciences. It is also strongly encouraged that BRS provide clarity into how it performs a risk assessment for each specific modified microbe to assure developers it is not regulating on potential and/or perceived risk, but on actual, documented risk.

Question 2: Describe areas where the clarity and/or efficiency of regulations governing modified microorganisms could be improved (e.g. definitions that need to be provided or revised, barriers to obtaining the data necessary to achieve commercialization).

BPIA RESPONSE: There is a need for Agency alignment and a clear pathway to non-jurisdiction or no permit required status from both BRS and USDA-APHIS-PPQ (PPQ). The "Am I Regulated?" (AIR) process served as a useful tool for developers to inquire as to whether a product was subject to regulation by BRS. With this process no longer available, developers do not have a formal process outside of a permit application submission to determine if the microbe is regulated or not. The lack of this process, or a similar one, can lead to inefficiencies with both the Agency and developers. Further, it is requested that modifications that are already exempted from previous determinations be grandfathered in. Continually re-assessing past determinations leads to more work and confusion amongst the regulated community as to whether products are or are not subject to regulation.

Additionally, it is desirable for BRS to look at its own Regulatory Status Review (RSR) program used for plants and consider an RSR-like process for microbes. In the development of this RSR-like program, BPIA recommends that APHIS establish clear, unambiguous criteria that will help developers understand how BRS is making its determinations of regulated and non-regulated status for each microbe that is evaluated. Clear criteria are especially critical as new species are being discovered with little to no literature history to establish their potential to be a plant pest.

Moreover, developers need clarity regarding the definitions used in the regulations, specifically what constitutes a "*plant pest*," "*plant pest potential*," "*persistence*," "*presence*," and "*biocontrol*." Ambiguity in the definitions codified in 7 CFR Part 340 make it challenging for a developer to determine whether its product meets the definition of plant pest or has the potential to pose a plant pest risk. Developers must therefore bring every candidate product to the Agency for a jurisdiction determination. This *de facto* requirement adds both resource and time burden on both BRS and the developer while clearer, more precise definitions with examples could provide more opportunities for developers to self-determine the regulatory status of their microbial products, while only enlisting the Agency to validate their determination in a process that would be similar to the now discontinued "Am I Regulated?" process.

Furthermore, clarity is needed between roles, responsibilities, and terminologies of USDA, EPA, and/or FDA. First, there needs to be clear criteria to determine when and how to engage with each regulatory agency, especially when a product may be subject to multiple regulations, as we see with pharmaceutical products and microbial pesticides that may also be plant pests. Having more than one Agency regulating a product type can be confusing and burdensome, both to the developer as well as the individual program offices reviewing these products for potential commercial release. A particular source of contention ensues when multiple agencies each require program-specific data submission and review for similar data requirements, creating redundancy and a waste of time and resources for all interested parties. Case in point, EPA's TSCA program requirements overlap substantially with those of BRS. Unfortunately, the current state of affairs requires developers to engage with both agencies and address each agency's review needs, though similar in scope, before they can test, much less commercialize their products.

Therefore, BRS, along with its partner program offices and other agencies, needs to focus on how to gain efficiencies between individual program/agency requirements. BRS and its partners should seek ways to ensure that data reviewed by one program/agency is provided to the next program/agency. Additionally, the agencies can acknowledge data reviewed and accepted by another program/agency (agency A) will not need to be re-reviewed

by program/agency B. Having such a streamlined, seamless process will inform all relevant programs while saving time and money for all concerned. An example of how this approach works well today is how most US states accept US EPA's review of new pesticides. Most states will not require another review within their state lead agency and will generally rely on EPA's review. Most states will instead only require a registration that can be as simple as a filed form, product label, and a registration fee.

This is in contrast with the current sequential review process that can occur when multiple agencies are involved in regulating a product, such as Endangered Species Act (ESA) Section 7 consultation reviews under FIFRA, the Clean Water Act (CWA), and other federal statutes. This often takes years to accomplish, with the net result of greatly delayed regulatory approvals.

BPIA suggests that the process be streamlined with a centralized submission portal allowing for a singular dossier submission that allows all relevant program offices/agencies to have access to the submitted information. This will allow each program office/agency to evaluate the relevant information for what products it regulates into its reviews and decisions. This centralized submission portal and approach would simplify the process, provide the same information to all parties that need to see it, and result in a more streamlined and coordinated response across all relevant regulatory agencies. This could build on the recent "decision tree" beta test organized by the Office of Science and Technology Policy (OSTP) and the Science and Technology Policy Institute (STPI), in which several BPIA member companies participated. While it is not a submission portal, it sets the groundwork for what a coordinated submission process could look like. BPIA applauds this type of intergovernmental cooperation, and we strongly suggest that this work be continued and expanded.

Consideration for process improvements should also include looking at how other countries deal with these jurisdictional nexi. For example, Canada, Brazil, and Argentina each have a clearer path to market for biopesticide products containing modified microbes. Looking specifically at Canada, the guidance provided by PMRA (Pest Management Regulatory Agency) and CFIA (Canadian Food Inspection Agency) is well-defined on each agency's website, laying out a clear path and providing explicit details on how products are regulated according to each agency's legal mandate and jurisdiction. The US approach should draw from the available guidance from these countries and attempt to harmonize with these approaches and data requirements as much as possible.

Additionally, there needs to be coordination and clarity surrounding regulatory and statutory definitions of terms used by each program office. Lack of definition alignment between agencies can be confusing for stakeholders.

Question 3: Describe key elements of a regulatory framework that would enable a scientifically sound assessment of a modified microorganism's plant pest risk, in order to inform regulatory decision-making by APHIS.

- *a. Describe any biological features of microorganisms that APHIS should consider when determining whether a modification changes the plant pest risk, and thus the regulatory status of a modified microorganism (e.g., the potential for horizontal gene transfer, the production of airborne spores, its ecological role, or the ability to remain dormant for long periods of time).*
- *b. What criteria, data, and information should be considered when assessing a modified microorganism's plant pest risk?*
- *c. What should APHIS consider when determining whether modification of a biocontrol organism could result in it posing a plant pest risk? Provide scientific evidence to support which types of biocontrol organisms and methods could or could not pose a plant pest risk.*

BPIA RESPONSE: BRS should consider a tiered RSR-like process approach in its regulatory assessment of microbes This process should include a list of exemptions from regulation, and the use of novel approaches to evaluate appropriate risk should be encouraged.

Further, BRS should regulate products based solely on whether the end products themselves are plant pests or pose a plant pest risk. If the introduced modification(s) expressed in the modified microbe is (are) not from a plant pest, and/or not increasing the plant pest potential of the microbe, BRS should exempting such a microbial product from the need of a movement permit.

Answers to specific subparts of the question are presented below by corresponding paragraph lettering.

a. APHIS should consider the intended use of the modified microorganism and should apply 'right-sized, risk-based' conditions on their permits. For example, modified microbes that are intended for laboratory assays only should not require a permit or, at a minimum, not have the same permit conditions as a microbe developed and targeted for field release.

b. If BRS has determined the modification(s) to a microbial product has not increased the plant pest risk of the wild-type microbe that PPQ has determined to be a plant pest, then BRS permit conditions for release should be on par with PPQ's 526 permits. Adopting the typical BRS permit, with its onerous and stringent protocols (including, but not limited to buffer zones, tracking, etc.), is not appropriate given the modified microbe is not any more of a plant pest than the wild-type comparator that PPQ would regulate. In this example, a BRS permit adds many more requirements than its wild-type parent would require under a PPQ permit for modifications that are low risk and not regulated by BRS. Such regulation is overly burdensome and does not contribute to environmental safety or to promoting use of products of biotechnology as required by EO 14081.

   Another point to consider is route of release. If the organism is not intended for release into the environment and will only be used in a laboratory setting, onerous permits should not be required. Risk assessment should consider the relative level of risk by intended use: laboratory risk < greenhouse risk < field release.

   A similar example is using a by-product of a modified organism. In this case, if the by-product is imported to make an end product and that end product is not itself a modified organism, a special import should not be required, especially if the modified organism is not intended for movement into the environment. The product being imported is what should be evaluated for regulation, not the intermediate use of the modified microbe that is not intended for import.

c. The crux of the evaluation of whether a modified organism poses a plant pest risk is to consider the product (and how it will be used in the field), not the process. Similar to what was stated in response to **PARAGRAPH B**. above, if the end product itself is not subject to regulation, the modified organism, which is not, in fact, being imported or released, should not be regulated. Alternatively, if the modification is not increasing plant pest potential, such as a PPQ-regulated organism modified to increase phosphate production, BRS should adopt permit conditions similar to that of PPQ.

   Additionally, as BRS re-evaluates its permitting approach, it should consider adopting a tiered approach that factors the types of modification(s) being introduced to the microbe, such as gene editing (small nucleotide changes), gene knock-out, intraspecies insertions, or intragenic insertions. Brazil and Argentina are good examples of how requirements can be proportional to the modification risk. This will minimize the regulatory burdens placed on microbes that would otherwise be appropriately regulated under PPQ's simplified permit conditions.

Question 4: How should modified microorganisms with multiple uses (e.g., developed for both biomedical or pharmaceutical purposes and agricultural purposes) be regulated and evaluated by APHIS? What steps should APHIS take to ensure efficient and appropriate oversight and evaluation when a product is subject to regulation and review by both USDA and another Federal agency?

BPIA RESPONSE: BPIA touched on this in our response to **QUESTION 2** above. The regulation and use of new biotechnology products is confounded by the fact that oftentimes, multiple agencies have jurisdiction. This is why it is critically important that APHIS along with FDA and EPA utilize the *Coordinated Framework* efficiently, effectively, and without undue burden to regulated parties. For example, plant pest products intended for biocontrol purposes are simultaneously regulated under PPA and FIFRA; plant pests regulated by PPQ may be further regulated under the Plant Quarantine Act; and plant pests with pharmaceutical agents are subject to both PPA and FDA's purview under FFDCA. A crucial component to an effective framework is achieving government efficiency and reduced regulatory burden, while ensuring public/environmental benefit and safety under the regulatory oversight of one program offices or federal agency. It will be important to consider how agencies are coordinating efforts in overlap areas to minimize resource inefficiencies and regulatory redundancy.

Clearly delineated roles and responsibilities need to be established for USDA, EPA, and FDA that align to the needs and requirements of each agency's program needs and statutory authority. Criteria must be developed to determine when and what each agency is regulating. Utilizing Memoranda of Understanding (MOUs) or Memoranda of Agreement (MOAs) are useful tools to establish jurisdictional roles and processes. One such example of an effective MOU is the FDA-EPA-USDA collaboration to review safety for agricultural chemicals that are also "medically important." A similar MOU and multiagency review panel could be established for "dual use" modified microbes.

Coordinating terminology and definitions among the program offices/agencies is also important to ensure that interpretation and understanding is the same across regulatory programs. So too are achieving efficiencies in process between individual program/agency requirements through data collaboration and sharing. In formulating the coordinated framework, a decision tree may provide transparency as to who "owns" the product from a regulatory and jurisdictional perspective.

The Agencies (USDA, EPA, and FDA) should create a streamlined approach for regulation through one agency, not a confusing puzzle of regulations that could potentially lead to sequential multiagency review. As mentioned above, this can be defined in MOUs if there is overlap. Creating such a "one-stop-shop" addressing the needs of all relevant programs will go a long way to improving the efficiency and efficacy of the current system. Within APHIS itself, it is crucial to better understand the alignment between PPQ and BRS functions.

Question 5: Should APHIS consider risk-based exemptions for certain types of microorganisms, or for certain modifications in microorganisms? If so, please provide examples of the types of modified microorganisms that should be exempt from regulation and provide scientific evidence to support which modifications and types of microorganisms should or should not be exempt.

BPIA RESPONSE: BPIA strongly supports the establishment of risk-based exemptions for qualifying microorganisms and/or modifications thereto. The following categories of modifications in which neither the donor nor host microorganism is a plant pest should be exempt from regulation:

- Changes in genomic DNA to modulate expression or regulation of existing native genes
- Introduction of genes, associated regulatory sequences and/or gene products from donor organisms that come from the same genus and/or species
- Introduced genetic material consisting of only well-characterized, non-coding regulatory regions from another genus
- Consistency for plants and microbes (*i.e.*, modifications that are already exempt for plants should likewise be exempt for microbes)
- Utilize determinations under AIR ("Am I Regulated?") process to compile an initial list of allowed microbes (similar to what was done in 7 CFR Part 340 for plants)
    - Modifications that are already approved from previous determinations must be grandfathered in, including the end product.
- Any organism where PPQ issues a Letter of No Permit Required (LNPR) or Letter of No Jurisdiction (LNJ) so long as the proposed edits are lower risk and are not coding for plant pest activity
- Any modification not coding for a functional plant pest
- Modifications that will only be used in labs or other contained facilities

Question 6: Are there any other specific issues or topics APHIS should consider in developing a regulatory framework for assessing the plant pest risk of modified microorganisms, or possible pathways to commercialization for modified microorganisms?

BPIA RESPONSE: The following should be considered during the regulatory framework development process for microbial biotechnology products.

- APHIS should weigh the risk/benefit of all permit conditions so that they are line with science-based risk of microbial products requiring permits. For example, post-harvest field destruction/burn down could cause more damage to soil health. This can be perceived as an extreme measure to destroy microbials, which may not pose any appreciable environmental risk in the first place.
- There needs to be more clarity on the path to commercialization from both PPQ and BRS.
- Stakeholders need BRS to provide clear and unambiguous guidelines, based on data, science, experience, and rational risk as to how they make their plant pest determinations. Under the current process, the Agency is taking an overly broad interpretation of its regulations (direct/indirect plant pest risk) and is exceptionally conservative in its evaluations, rendering most microbes as plant pests.
- MOUs should be updated and/or developed between BRS and EPA that clearly delineate who has jurisdiction in which instances, so to the extent possible, products are not simultaneously regulated by both agencies.
- BRS and EPA need to bring in PPQ to support better alignment amongst the agencies and allow for more streamlined discussions regarding modified microbes with pesticidal intentions.

CONCLUSIONS

In summary, BPIA has highlighted a few key considerations for new and emerging technologies utilizing modified microbes. We appreciate the opportunity to comment and offer support to USDA-APHIS-BRS concerning this topic. We look forward to working together to craft a solution that meets the needs of the statute while recognizing the unique nature of these new, innovative biological agricultural input products. BPIA welcomes further engagement with APHIS. Should you have any questions about this response, please feel free to contact me.

Sincerely,

BIOLOGICAL PRODUCTS INDUSTRY ALLIANCE

Keith J. Jones, Esq.
Executive Director