

GUIDE FOR SUBMITTING PERMIT APPLICATIONS FOR MICROORGANISMS DEVELOPED USING GENETIC ENGINEERING UNDER 7 CFR PART 340

RESPONSE TO COMMENTS

On March 23, 2023, APHIS BRS released a draft guide for submitting permit applications under 7 CFR part 340 for microorganisms that have been developed using genetic engineering. BRS invited the public to review and comment on the draft, resulting in feedback from 24 individuals and organizations (one organization’s letter contained 2,149 undersigned names). This document summarizes and addresses the comments BRS received on the draft guide and clarifies whether any changes were made based on the feedback received.

We received comments on a range of different issues and grouped the comments into the following categories:

- Permit application data requirements
- Principle risk proportionality when determining data requirements
- Permit requirements when conducting research in a contained facility
- Coordination among regulatory agencies
- Clarification on modified microbes that are excluded or exempted from 7 CFR part 340

Beyond these categories, we also received comments related to how BRS verifies the information in permit applications, enhancing the Standard Operating Procedures (SOPs) that accompany permit applications, and requests for establishing a Regulatory Status Review (RSR) along with regulatory exemptions for modified microbes to support their commercialization.

Comments about labelling and general comments about ecosystem service provided by microbes are out of scope for the guide, and BRS will not address them here.

Comments about permit application data requirements

1. Commenters asked BRS to clarify the data requirements for obtaining a permit for field trials; others said BRS should require more data and conduct a thorough environmental analysis before issuing a permit.
2. Commenters expressed the concern that BRS requires too much data and information in permit applications.
3. Some commenters believed the processing time for permits was too long, including delays associated with incomplete submissions. Conversely, one questioned whether a 45 day-time frame is adequate to review an import and/or interstate movement permit.

Response:

The USDA established biotechnology regulations in 1987 and has made seven amendments since then. The regulations require similar information for both plant and non-plant organisms, including microbes, for both shipments and environmental releases to assure their containment or confinement. For example, all applications to move a modified organism must include information on the molecular change, trait, and the method of shipment to ensure the organism is securely contained. Likewise, applications for permits involving environmental releases must include information on the molecular change, traits, and the procedures the developer will use to ensure confinement to prevent the escape, spread, and persistence in authorized locations. The data requirements for permits are tailored to support the Plant Protection Act’s protection goal of preventing the unauthorized release of regulated materials into the environment.

Our experience with both plant and non-plant organism permits indicates that early consultations with BRS about planned research and permit requirements, along with timely submission of the necessary information, are crucial to achieve timely permit issuance. During consultations involving modified microbes, BRS and developers review a summary of the information requirements for the permit application. Developers have reported that these consultations make it easier for them to meet the permit application requirements. We have incorporated this information into the guide because of its utility to developers and interested parties. These consultations, together with guides and other information available on our website, are intended to help first-time and returning permit applicants navigate the permitting process and improve the efficiency of the permitting process. Finally, BRS has reorganized the guide to highlight required information in the main body of the document and placed the probing questions developers should think about when developing SOPs (“considerations”) in the Appendix to make clear that answers to these questions are not part of the permit application. In terms of commenters who believed we should require more information on permit applications, based on our experience, we believe the permit application and accompanying SOPs provide adequate information for BRS to establish any necessary supplemental permit conditions to ensure the containment or confinement of modified microbes.

4. Some commenters noted that revisions to regulations and guidelines for organisms developed using genetic engineering can be unexpected for applicants who are familiar with legacy regulations and previous guidelines. Other commenters noted that the approval process for permit applications can take several months or even years, depending on the complexity of the application and may require further information, which may surprise applicants who are expecting a faster approval.

Response:

As noted above, BRS established biotechnology regulations in 1987 and has revised the regulations seven times since then. When undertaking a revision, BRS uses notice-and-comment rulemaking to ensure the public has an opportunity to review and provide feedback on a proposed rule before USDA issues and implements a final rule. With the most recent regulatory revisions (the most significant update since 1987), BRS used a phased approach to implementing the revised regulations to allow developers time to update and align business processes with the revised regulations. BRS also maintains a stakeholder registry and uses this tool to share regulatory and process updates to avoid surprise and ensure stakeholders have an opportunity to visit with BRS and ask questions related to the revised regulations.

Regarding permit timelines, the regulations specify that a permit application for shipment will be approved within 45 days, while field release applications may take up to 120 days. Delays can occur if a permit application does not contain the necessary information, which can prolong the review and issuance process. The purpose of the guide is to support developers in providing complete permit applications when they first submit them to enable efficient and timely review.

5. Some commenters suggested that BRS consider the potential for horizontal gene transfer (HGT) between microbes when evaluating the environmental risk and worry the permit guide may not adequately address the long-term impact of microorganisms on the environment or the risk of HGT to other organisms.

Response:

BRS considers the potential for horizontal gene transfer (HGT) when evaluating microbe permit applications. For example, BRS considers whether the modification to the microbe is associated with

fitness-enhancing traits. In this context, BRS considers the circumstances that may present a potential plant pest risk and tailors the permit conditions to prevent such risks. Permit conditions require that all modified microbes in confined field trials, including those that received modified traits through HGT, should not persist or spread from the regulated field trial at its conclusion. If spraying modified microbes onto plant parts poses a potential risk of insect vectors transmitting the modified microbe to nonregulated plants and facilitating HGT between modified and wild-type microbes, the permit conditions will include measures to prevent vector transmission.

Comments about the Principle of Risk proportionality when determining data requirements

1. We received a comment that BRS' approach to regulating microbes under 7 CFR part 340, is overly cautious, leading to duplication and inconsistency with other agencies such as such as Plant Protection and Quarantine (PPQ) and the U.S. Environmental Protection Agency (EPA).
2. Another commenter asked BRS to find ways to acknowledge these sister agencies' evaluations to reduce duplication and ensure that permit conditions are based on clear risk evaluations. The organization asked BRS to define the data and information required for field release permits to focus on actual (rather than hypothetical) risks and encouraged BRS to allocate sufficient resources to develop a process based on objective scientific criteria that provides a regulatory offramp for microbial products, if warranted.

Response:

BRS and EPA have separate regulations for modified microbes. BRS focuses on assessing whether the modified microbes pose an increased plant pest risk compared to their original form, while EPA regulates modified organisms intended for pesticidal purposes under the Federal Insecticide Fungicide and Rodenticide Act (FIFRA) and the Federal Food Drug and Cosmetic Act (FFDCA), or if used as biofertilizers, bioremediation agents, and for the production of various industrial compounds, including biofuels under the Toxic Substances Control Act (TSCA). Although some data requirements may vary based on agency specific regulations, we agree there is an opportunity for greater alignment. In addition to continuing to hold regular meetings to share information about modified microbes under each agencies' review, BRS will work with EPA to streamline and align its data requirements where possible. To allow this work to proceed, BRS is posting this guide as a second draft and in the future will refine, as possible, information requirements for permit applications.

3. A commenter stated that BRS' current regulation of modified microbes captures products outside the scope of the agency's authority under the Plant Protection Act, imposes burdensome and inflexible field trial conditions and requirements that increase research and development costs, and provides no regulatory off ramp for oversight under 7 CFR part 340. Other comments shared the concern that BRS' revised regulation do not provide a comparable pathway for the commercialization of modified microbes like Regulatory Status Review or (RSR) or Confirmation of Exemption Request (CR) does for modified plants.

Response:

BRS' regulation of modified microbes is based on the Plant Protection Act's authority to regulate plant pests and biological control organisms intended to control plant pests. This includes genetically modified biological control organisms that could harm non-target beneficial organisms such as invertebrate predators, pollinators, or microbes that promote plant health. As these organisms are introduced into the environment, we must consider both their direct and indirect effects on non-target organisms that are beneficial to agriculture. If a modified organism is known to have harmful impacts on beneficial non-target organisms, it is within APHIS' authority under the PPA to restrict its release. If there is uncertainty

regarding the organism's impact on beneficial non-target organisms, BRS may regulate its movement and release until there is a better understanding of its effects.

With that said, to further address the concerns, BRS will explore potential regulatory changes that would exempt from 7 CFR part 340, in whole or in part, modified biological control organisms that are not plants 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. BRS will also explore potential mechanisms for risk-based de-regulation of non-plant organisms that could be proposed in future rulemaking, including by considering comments from stakeholders on the [draft guide](#), the [Request for Information](#) associated with Executive Order 14081, and further engaging developers and other stakeholders.

4. A commenter raised concerns about BRS' interpretation of its authority under the Plant Protection Act regarding microbes noting that, in the past, the regulations listed the organisms that were considered "plant pests." The commenter noted that the current 7 CFR part 340 lacks clear guidelines and instead relies on undefined criteria, leading to a more precautionary approach rather than a risk-based one. The commenter asked that BRS use more concrete sources of guidance, such as the criteria used by PPQ, to improve transparency and clarity.

Response:

In the legacy biotechnology regulations, BRS 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 BRS updated its regulations in 2020, it removed this listing from the regulations because it had become out-of-date. BRS 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, BRS agreed to post a list of taxa on its website that could be regularly reviewed and updated. We agree that the availability of this plant pest taxa list plays an important role in providing clarity on BRS regulatory scope and permitting requirements. BRS will partner with subject matter experts to develop, maintain, and update a plant pest list. BRS plans to implement its partnership and begin development of the plant pest list in fiscal year 2024.

Additionally, BRS collaborates with PPQ to determine the plant pest status of wild-type microbes before deciding the plant pest status of their modified versions. PPQ and BRS have established a working group to address areas of ambiguity related to a microbe's regulatory status, with a goal of harmonizing, as possible, information and data requirements for modified and non-modified microbes regulated under the Plant Protection Act. In cases where the taxonomic identity is unclear, BRS also refers to peer-reviewed scientific literature or the latest standards used by scientific societies to determine the plant pest status of the modified microbes.

5. Some commenters have requested that BRS postpone the finalization of the draft guidance until it has consulted with more stakeholders. They also suggested revising the guide to be more in line with BRS' policy of making regulatory decisions based on scientific evidence.

Response:

We agree that further coordination and clarification must occur before BRS can finalize the guide. For this reason, BRS is posting a second draft version. We have also updated the guide to indicate that applicants can submit multi-year (2-3 years) permit applications for importation and interstate movement of modified microbes and can submit permit applications for importation and interstate movement of bacteria and fungi at the genus level. Since 1987, APHIS has issued more than 5,200 permits and acknowledged more than 14,000 notifications for interstate movement and importation

activities with modified organisms. Over this period, APHIS has rarely observed breaches in containment or accidental release of regulated material during shipment. Additionally, within APHIS, PPQ issues three-year permits for the importation and interstate movements of non-modified organisms, and the Preamble to the 2020 revision to APHIS' biotechnology regulations specifically noted that the revised regulations allow multi-year permits for modified organisms. Limiting permits for interstate movement and importation of modified organisms to one year had significantly burdened the regulated community. Developers had to submit repeated applications to move material between locations. Such activities also placed a resource burden on BRS, when conducting reviews and authorizing shipments every year, even though the regulated activities had low-risk potential. Issuing multiyear permits for interstate movement and importation of modified plants, microbes, and insects reduces a significant burden for the regulated community and BRS, saving applicants time and resources, and allowing for risk-proportionate regulation for this type of activity. APHIS considers individual circumstances when deciding an appropriate duration for each permit. Applicants will be able to seek permit amendments to address changes in planned research.

BRS is also clarifying that species belonging to the same genus can be included within a single importation or interstate movement permit application if containment protocols are appropriate for all species and they remain securely contained during shipment. BRS has previously issued permits for multiple species that share biological traits that enable similar containment protocols, and PPQ issues permits for multiple microbe species at higher taxonomic levels. BRS is limiting permit applications to the genus level in order to facilitate timely permit approval given the larger number of constructs that could be included in a permit application for higher taxonomic levels and the time it would take to review a larger application. In the future, after BRS updates this draft guide to further address comments from stakeholders on the [Request for Information](#) associated with Executive Order 14081, BRS will, at that time, take additional public comment.

Comments regarding the need for better coordination among regulatory agencies.

Commenters requested better coordination among regulatory agencies to streamline the data requirements. They would like to see more communication between BRS and EPA to reduce confusion over which rules and regulations apply, particularly if there is conflicting information.

Response:

As noted above, we agree that additional coordination and clarification would be helpful. Although we routinely meet with both PPQ and EPA, BRS will work with PPQ and EPA to streamline and align data requirements where possible. To allow for this work to proceed, BRS is posting this guide as a second draft to support current applications for permits and, in the future, will provide more clarity on information requirements for permit applications, among other things.

Comments about adding permit requirements for conducting research in contained facilities

1. Multiple commenters expressed the concern that a modified microbe does not require a BRS permit if the experiment for the microbe is conducted in a contained facility. These commenters opined that BRS should require permits for contained facilities to prevent accidents and ensure facilities are truly suitable for working with microbes, and to oversee novel microbes.

Response:

Under the Plant Protection Act, BRS has authority to regulate the importation, interstate movement, and release into the environment of certain modified microorganisms. 7 U.S.C. §§ 7711 and 7712. Activities

that do not fall within those categories – like research in structures that meet the criteria of a “contained facility” as defined in the regulations – fall outside of the scope of the Plant Protection Act and 7 CFR part 340. We appreciate the commenters’ concerns about ensuring the safety of research activities in contained facilities. When reviewing an application for importation or interstate movement of a modified microbe, we ensure that the receiving facility is adequate to ensure containment of the microbe. In the guide, we explain that a BRS permit is not required if a developer is creating a modified microbe and conducting research activities involving that modified microbe in an area meeting the definition of “contained facility” (that is, a “structure for the storage and/or propagation of living organisms designed with physical barriers capable of preventing the escape of the organisms”) without importing the microbe or moving it interstate. To ensure a facility prevents the unauthorized release of a modified microbe, we provide developers with resources they can use to ensure containment appropriate for their microbes. If a developer is unsure whether their contained facility is adequate to prevent the escape of a modified microbe, we encourage them to apply for a permit so that we can assist them with assessing their facility and determining whether the facility meets the criteria for a “contained facility” or whether they require a permit. We suggest this approach to help developers mitigate against noncompliance with the regulations resulting from the unauthorized, accidental, or inadvertent release of a modified microbe subject to 7 CFR part 340, which could result in enforcement action, including the assessment of civil penalties.

2. A commenter emphasized the importance of Standard Operating Procedures (SOPs) when submitting a BRS permit through the APHIS eFile system. In addition to movement, the point of origin, and release conditions, the conditions under which the experiments should be performed should also be part of the SOPs.

Response:

The guide provides information to permit applicants and holders on how to keep modified microbes contained and secure to prevent any unintended release or spread in the environment. The guide covers different containment conditions, we have incorporated a checklist for facility inspections into the guide, and we thoroughly review SOPs to ensure proper procedures are in place to maintain confinement and prevent unauthorized release or spread of modified microorganisms in the environment.

3. One commenter expressed concern regarding trial termination and procedures to effectively stop persistence of the modified microorganism in the environment.

Response:

Trial termination is a specific term relating to the release of modified microorganisms authorized under a BRS permit. In the guide, we discussed trial termination to assist permit holders in understanding their obligation to terminate their trial in a way that prevents unauthorized release, spread, dispersal, and/or persistence of the modified microorganism in the environment.

Comments regarding why certain microbes are exempted from regulations.

1. One commentator requested clarification of why we use the term “exemption” (rather than exception) when describing modified microbes that are registered with EPA and, thus, are not required to follow BRS’ permitting requirements. The commenter noted that microbial pesticide labeling should not be a defining factor in determining movement in and outside the environment. Another commenter pointed out that that some organisms (for example, agrobacterium) are exempt from the permitting requirements in 7 CFR part 340, while others are not, and wanted to understand the basis for and scope of this exemption.

Response:

7 CFR 340.5(f) indicates a permit is not required for the movement of any GE microorganism product that is currently registered with the EPA as a microbial pesticide, so long as the microorganism is not a plant pest as defined in § 340.3. Although BRS and EPA operate under different statutory authorities, they consider similar factors when evaluating a modified microbe’s risk. Since EPA’s review includes areas of concern to BRS, BRS recognizes EPA’s review and registration of a microbial product to avoid redundant regulation and allows the agencies to make the best use of limited resources. BRS used the term “exempt” from regulation because the permitting requirements apply to microbial pesticides unless the product is registered with EPA. If, for example, the microbial pesticide was no longer registered with EPA, the developer would be subject to BRS’ permitting requirements for importation, interstate movement, and environmental release. For additional information on whether a modified microbe is subject to 7 CFR part 340, please visit our [questions and answer webpage](https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/guidance-documents/qa-table/brs-qa) <https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/guidance-documents/qa-table/brs-qa> and filter by “microbes”.

Regarding the request that we clarify the basis for the exemption for disarmed *Agrobacterium* species, historically, these bacteria have been regulated and required permits for their interstate movement due to their classification as plant pests. However, disarmed *Agrobacterium* species lacking disease-causing ability have been used as a tool to modify organisms for several years now. The interstate movement of these disarmed *Agrobacterium* species has not resulted in the dissemination of plant pests within the United States, and the plant pest risk associated with them is very low. Moreover, there are safeguards in place that can effectively mitigate those risks. Therefore, for the reasons mentioned above, the interstate movement of disarmed *Agrobacterium* species is exempt from permit requirements.

2. A commenter suggests that BRS make it clear that microorganisms used for biocontrol, which do not present any risk to plants, do not need a permit.

Response:

The revised regulations require a permit for a modified microbe that is intended to control a plant pest and could pose a plant pest risk. The revised regulations do not require a permit for a biological control organism that does not pose a plant pest risk and is not a plant pest. As we noted in the preamble to the [May 2020 final rule](#), “We agree with the first comment (i.e., that organisms and microorganisms used to control plant pests should not require regulation if they are not plant pests themselves or do not pose a plant pest risk), and this rulemaking does not provide for the regulation of biological control organisms if they are not plant pests themselves or do not pose a plant pest risk.”

Miscellaneous comments

1. A commenter stated that BRS overlooks the majority of gene edited microbes, including those created with CRISPR technology, which, according to the commenter, will likely produce the most diverse range of genetically modified microbes in the future.

Response:

The definition of “genetic engineering” in [7 CFR part 340](#), includes genome editing, and our risk assessment is based on the characteristics of the modified organisms (that is, whether the new trait could pose a plant pest risk). This is known as product-based regulation. Under the revised regulations, BRS does not consider whether the microbe was modified using genome editing or a different method of biotechnology when evaluating whether it is subject to the regulations.

2. Some commenters expressed concern about how BRS verifies the information provided in permit applications.

Response:

When considering an application for importing, moving interstate, or releasing modified microorganisms, BRS carefully evaluates all provided information. Once a permit is issued, we are confident that the permit conditions and SOPs describing how the developer will meet the permitting conditions will prevent any unauthorized release or spread or persistence in the environment. Additionally, BRS conducts regular inspections of the facilities and field trials of permit holders to ensure that they are following the permit conditions and associated SOPs.

3. A commenter recommended that BRS consider additional information, such as the identification of the biological properties of a species, when conducting a permit review to ensure organisms are properly evaluated and to assess any potential negative impact it may have on other organisms.

Response:

The guide outlines comprehensive data requirements that BRS considers when evaluating permit applications. Permit applications must include all the required technical information before BRS evaluates and issues a permit. Part of this evaluation includes assessing the properties of all species listed in the permit applications. Most of the microbial species listed in permits are well-known to BRS and within the research community. If a new species is listed in a permit, we work with the applicant to gather literature and ensure that the permit contains appropriate conditions to ensure the modified microorganism will not be released, spread, dispersed, or persist in the environment.

4. A commenter has expressed concerns that the regulatory monitoring of modified microbes under 7 CFR part 340, may not provide adequate environmental protections and does not allow public review and comment related to permit applications, which limits stakeholders in voicing concerns about the release or introduction of modified microbes.

Response:

BRS follows APHIS National Environmental Policy Act (NEPA) Implementing Regulations ([7 CFR part 372](#)) when evaluating permit applications and establishing permit conditions to ensure containment or confinement of a modified microbe. Modified microbes often share many of the same biological characteristics as those of well-known microbes that APHIS is familiar with, and BRS has experience establishing permit conditions that have successfully contained and confined modified microbes, confirmed through compliance inspections. In most of these instances, an environmental assessment or environmental impact statement that is subject to public review and comment is not required under APHIS' NEPA Implementing Regulations. If a confined field release of modified organisms involves new species or organisms or novel modifications that raise new issues, or the release is not confined, BRS will prepare an environmental assessment or an environmental impact statement for public review and comment.