BRS Regulatory Status Review Webinar
September 28, 2021
Questions and Answers

If a new Plant-Trait-Mechanism of Action (PTMOA) combination is found to have no possible pathways to increased plant pest risk after the initial review, will APHIS publish the Regulatory Status Review (RSR) and/or the response letter on their website or simply update the PTMOA table?
Yes. When we determine that a plant is not subject to the regulations, we will post the PTMOA on our website, on the PTMOA table. We will also publish the incoming RSR request and the determination letter we send to the requester, with Confidential Business Information (CBI) redacted.

What is the timeline for providing scientifically valid evidence for APHIS to continue the Plant Pest Risk Assessment (PPRA)?
There is no required timeframe for submitting evidence. At the conclusion of the initial review, the requester receives a letter from APHIS describing the plausible pathway(s) to increased plant pest risk that was/were identified. The letter also states APHIS has paused the review until the requester asks that we prepare a PPRA. Requestors can pause the process for as long as they wish if they are generating data to support a PPRA.

Given that new scientific data highlights that new gene-edited plants result in unintended on- and off-target impacts, the plant pest evaluation seems to be too narrow; is the scientific data that discusses on- and off-target unintended consequences sufficient for a re-review?
When genetic material is inserted into the plant, we review information related to the material that has been inserted or, if it has not been created yet, that is intended to be inserted. Likewise, when genetic material is edited, we review how the material has been edited or is intended to be edited. When looking at things like editing, we do consider very close homologous sequences in the genome (such as sequences in highly conserved gene families) to make sure the targets are specific and other areas of the genome are not (or will not be) modified.

We review information supplied by the developer and our own analysis to determine if other areas of the genome are edited, or likely to be edited, and will then use that information to determine if there is any plausible pathway to increased plant pest risk and, if we identify a plausible pathway to increased plant pest risk, to further conduct a Plant Pest Risk Assessment. If we find the modified plant is unlikely to pose an increased plant pest risk, our decision will explain the basis for our conclusions. Our decision will note that if developers at any time become aware of any information that may affect our assessment, they must notify us. Scientific data that generally discusses on- and off-target unintended changes is not sufficient for re-review. Rather, a request for re-review must be supported by new, scientifically valid evidence bearing on the plant pest risk associated with movement of the specific plant in question.

Are we able to get a list of attendees?
In keeping with our established practice, we are not providing the list of attendees.

There seem to be a lot of public comment submissions as form letters. Can those form letters be put into a file so we can view independent questions?
We see what you see posted on regulations.gov. The website currently does not have a way to put those letters in a file on regulations.gov so the public can view independent comments.

Would an exempt plant be allowed to be labeled as USDA organic?
The labeling of products is handled by our sister agency, the Agricultural Marketing Service, as a marketing component of the work we do here at USDA, so this is outside the scope of our regulations and is not something covered under 7 CFR part 340.

Could any of these plants be used in forestry practices for climate change?
There are products in development that we have not reviewed, so it would not be appropriate for us to opine on hypothetical questions. Genetic engineering can be used to develop a variety of traits, including those that adapt to climate change.

Are there agreements where some of the exempted plants might be grown on public lands?
When a plant is determined to be exempt from the regulations, APHIS does not have a regulatory role in where planting will be done.

Do you feel you could've done more to promote this meeting to the public?
We did our very best to publicize this meeting in a variety of different ways. We hear that you recommend we use more ways to touch a wider audience. We will think about additional methods we can use in the future.

How does the plant pest risk assessment address the process of modification, not just the final product, and how does it evaluate for on- and off-target unintended modifications both in the plant and in the ecosystem? How does this process address compounded impacts from stacked traits, such as herbicide tolerance with various chemicals?
Over three decades of experience has shown the process of modification does not in and of itself create plant pest risk; it is the characteristics of the final product that are important. Off-target modifications are discussed above. Regarding stacked traits, we would take the same approach with stacked traits that we outlined in the presentation for single traits, which is the problem formulation approach. We would identify whether there is any plausible pathway to increased plant pest risk. If it is a plant with stacked traits, the only additional thing we would look at is whether there are synergistic effects of these different traits. If not, we will have separate mechanism of action documents for each trait and perform problem formulations as if they are independent. When a plausible pathway to an increased plant pest risk is identified, we will undertake an appropriate environmental assessment as part of that analysis.

If under the insect-resistant corn example presented, the requester submitted Tier 1 safety data with the original submission, wouldn't that address your possible pathway to increase plant pest risk and therefore possible risk testing in step one, thereby not requiring the 15-month process?
No, it would not. The purpose of the initial review and the purpose of the Plant Pest Risk Assessment (PPRA) are very different. The purpose of the initial review is problem formulation, where we are identifying any plausible increased plant pest risks that would be appropriate to analyze for that plant. We are setting the scope of the analysis that needs to be done, not thinking about whether data already exists that might address those plausible pathways to increased plant pest risks and allow us to get to the conclusion of that analysis. The risk analysis phase is the PPRA, and this step includes public comment on the draft assessment. In addition, it is important that the Agency has an opportunity to independently perform problem formulation. A developer may not have identified all plausible pathways to harm or may have identified pathways that APHIS does not consider plausible. If requestors anticipate that a PPRA will be required, they are welcome to start acquiring and assembling additional data and information of their choice prior to our completion of Step 1 so that it is ready for rapid submission upon completion of Step 1.

Do all elements need a nucleotide sequence identification number, or can a publication reference be provided that is specific to that element?
We request a nucleotide sequence identification number when available, we request an identification or accession number because a reference number will direct us straight to the sequence in public databases, which does not occur with a publication reference. Citations can be added to support the stated plant-trait mechanism of action but are discouraged for sequence information unless no other source of sequence information is available.

You said in the presentation that the sequence of the insert of the event is required for events with large inserts, however, the guidance says, "provide the nucleotide sequence of the inserted genetic material or the intended insertion." The use of the word "intended" makes me think that submission of the intended DNA—for example, a T-DNA sequence—is fine, which is consistent with earlier remarks that the Regulatory Status Review (RSR) is not event-specific. Am I reading the guidance correctly?
Yes. You are reading the guidance correctly. The RSR is not event-specific, and we need the sequence of the entire intended insertion. We want the sequence of what is intended to be inserted or is inserted but we do not need surrounding genomic data. This is why it is event-independent. We just want the sequence for the insert, not sequence information on where it is inserted into the genome.

If we haven't made the event yet and we want to submit a Regulatory Status Review (RSR) and we've sequenced the plasmid so we know what DNA we intend to insert, can we provide that as the sequence of the intended insertion?
Yes, you can provide the intended insertion. If we were to determine the plant is not be subject to regulation, our decision will note that if developers at any time become aware of any information that may affect our assessment, they must notify us.

If we submit a Regulatory Status Review (RSR) and the initial review says there's no plausible pathway to plant pest, I understood APHIS will publish the incoming request on the website, and when the initial step is done, APHIS publishes the response letter and the Plant-Trait-Mechanism of Action (PTMOA)?
When we receive a request, we do not publish it immediately. If we determine the plant is not subject to the regulations at the end of RSR Step 1, the incoming RSR request and the response letter will be posted to the website, with appropriate redaction of CBI. We will also post the PTMOA combination on the PTMOA table on our website.

Does the nucleotide sequence identification number provided need to be for the exact sequence of the event or is some variation in the sequence acceptable? For example, the actual element sequence has a few base differences, or is shorter than the sequence in the nucleotide sequence?
If your modification is a few nucleotides different from a sequence with a Genbank or other sequence identification or accession number, then please provide the identification or accession number and identify the sequence difference.

How long is the public comment period for the Plant Pest Risk Assessment (PPRA)?
Generally, there is a 30-day comment period for a PPRA.

On page 11, you are asking for one particular name for the insert component. This will not work for some components. Would it be possible to set a character limit for the description?
We currently do not have an electronic system for submitting Regulatory Status Review (RSR) requests. We will cross that road when we have an electronic system like the APHIS eFile system we have for permits. Right now, we are accepting RSR requests through the RSR email address (RSRrequests@usda.gov). In the case where a one-to-three-word name is not sufficient, certainly, a longer name can be provided, on a case-by-case basis. As short as possible description would be acceptable.

Is there an opportunity to address or refute possible pathways identified in the initial review so that a Plant Pest Risk Assessment (PPRA) is not necessary?
No, currently, we do not have such a process. The purpose of the PPRA is to address or refute the plausible pathways to increased plant pest risk identified in the initial review so any information that an applicant would want to submit to show that an identified plausible pathway is not a concern would be part of the PPRA.

Can you please clarify whether the Regulatory Status Review (RSR) process is optional or a mandatory step prior to the submission for deregulation?
The RSR process is not optional. Unless a plant is otherwise exempt, it is mandatory to submit an RSR request to determine if a plant is subject to the regulations. If we determine the plant is not subject to the regulations as a result of the RSR, our decision will indicate such status.

In the case of a Plant-Incorporated Protectant (PIP) trait, where would the description of the effective concentration and tissue concentration profile be placed?
For traits like pesticidal proteins, the tissue expression profile is important for understanding plant pest risk. In that case, we require developers to describe the maximum tissue expression profile for pesticidal protein as part of the Mechanism of Action (MOA). This is discussed in the guidance, and if you look at the published Plant-Trait-Mechanism of Action (PTMOA) table, there is a footnote that describes that we consider the maximum tissue expression profile to be part of the MOA for those traits.

I tried to submit a request two weeks ago. In the confirmation email, I received a web link, but the link was not valid, and I do not know if my request was received.
If for some reason the link is not working, please email the Regulatory Status Review (RSR) inbox (RSRrequests@usda.gov) and we will work with you to resolve the problem.

For plant incorporated protectants (PIPs) there can be a lot of overlap between data required by the Environmental Protection Agency (EPA) and APHIS. How much cross-collaboration occurs between agencies? Or is each review independent without collaboration or discussion?
For a PIP, USDA looks at impacts of modified plants on non-target beneficial organisms. EPA looks at the overall impact on the ecosystem or the organism of interest. Whenever we have a PIP, we always coordinate with EPA to understand each other's perspective and resolve any differences in the context of our respective regulatory roles.

Once an event has been deregulated, can it be stacked with any other deregulated event or should this still go through the review again?
Whenever a plant-trait-Mechanism of Action (MOA) combination is determined not to be regulated, you can use conventional breeding to add it to existing plant-trait-MOA combinations that are not regulated; you do not need to come back for review, as long it's a breeding stack. You would only come back for review if it is a molecular stack.

Six months after the implementation of the Regulatory Status Review (RSR) process for six crops, one has to assume that some submissions have occurred, and some may be nearing completion with no possible plant pest risk identified. Can BRS give us an update on the number of RSR submissions to date and whether some are nearing completion?
We have received a handful of RSR requests, and we anticipate receiving more as all plants are eligible for the process beginning October 1, 2021. We continue to process them within the timeframe of the regulations. We do not anticipate it taking longer at this time.

Should the introduced trait be intended to provide protection against heat, or cold and the specific plant species has no related wild species in the target production area(s), can the plant pest status be determined in an expedited manner?
We cannot predict the timeline for determining whether a plant is unlikely to pose an increased plant pest risk without looking at the specific plant, trait, and mechanism of action. Plants developed using genetic engineering that are submitted for a Regulatory Status Review (RSR)

will be examined in the initial review to determine if there are any plausible pathways to increased plant pest risk based on the combination of plant, trait, and mechanism of action. The initial review can take up to 180 days for a complete RSR request. If no plausible pathways to increased plant pest risk are found, the RSR concludes after the initial review, and the plant would not be subject to regulation. If plausible pathways to increased plant pest risk are found, a Plant Pest Risk Assessment (PPRA) would be required. The PPRA stage would take up to 15 months from the time the complete RSR request for the initial review was received, not counting any time the process is paused by the requestor.

Agronomic data was an integral component of the petition process. Why is this not a requirement for the Regulatory Status Review (RSR) process?
The RSR uses problem formulation in the initial review stage to focus the analysis on the plausible pathways to increased plant pest risk. Whether there is a need for agronomic data, and what agronomic data would be relevant, depends on the identification of plausible pathways to increased plant pest risk.

"Intended" is used in the language of Regulatory Status Review (RSR) submission, is there an opportunity to submit intended sequence changes for the RSR rather than the specific sequence alignments discussed in the guidance?
Intended modifications may be submitted for RSR, but if the intended modification is an edit, both the intended sequence and the alignment between the intended and the unedited sequence should be submitted, as described in the draft guidance. If the intended change is an insertion, then an alignment is not required, but the sequence of the entire insert should be included. If, as a result of the RSR, we determine the plant is not subject to the regulations, our decision will note that if developers at any time become aware of any information that may affect our assessment, they must notify us.

Are only nucleic genetic engineering modifications included in a Regulatory Status Review (RSR)? Mitochondrial? Or, any introduced epigenetic factors considered?
Modifications to any genome (e.g., nucleic, mitochondrial, chloroplast) are considered in the RSR. Epigenetic changes are not within the scope of the regulations and thus are not considered in the RSR.

To follow-up on the answer about on and off-target impacts: USDA's process seems to rely on the developer to provide sufficient data and scientific information about unintended consequences. How will the USDA ensure there is independent peer-review analysis, rather than relying on company data and review?
Developers are responsible for providing truthful and accurate information regarding their modified plants. Changes that could reasonably have been anticipated when using a particular method of genetic engineering must be described in the request. If they were present in a modified plant but not evaluated as part of the Regulatory Status Review (RSR) and could affect the outcome of the RSR, then the decision based on the RSR may not be valid for that plant. If, as a result of the RSR, we determine the plant is not subject to the regulations, our decision will

note that if developers at any time become aware of any information that may affect our assessment, they must notify us.

Random off-target modifications to a genome need not be described in the RSR request. Scientific evidence has shown that these types of changes occur at a similar frequency to changes that occur during conventional breeding and that they are not expected to increase plant pest risk relative to a conventionally bred comparator.

To confirm my understanding, the 15-month timeline for an RSR that goes through both Step 1 and 2 includes the time needed for a public comment period. Is APHIS thinking of a 30-day comment period?
Yes, the planned public comment period for the draft Plant Pest Risk Assessment (PPRA) is 30 days. The 15-month timeline includes the initial review stage and the PPRA stage, including public comment, and excludes any time the process is paused by the requestor.

Will Mechanism of Action (MOA) combinations determined to be exempted after a Regulatory Status Review (RSR) automatically be added to the exempted MOAs list, or is there a petition process to get new MOAs exempted?
Plant-trait-MOA combinations that are determined to be not subject to the regulations following the RSR will be added to the PTMOA table on the BRS website.

Please show me the legislation that protects developers from unintended consequences if found later in to have a negative effect.
With respect to the Plant Protection Act (PPA), there is no provision that protects developers; the PPA was enacted to protect plant health and agriculturally important resources. It would not be appropriate for us to comment on any other statutory provisions.

Based on the crops and traits BRS is familiar with, do you expect most RSRs to go to the second step (Plant Pest Risk Assessment (PPRA) stage)?
We expect that many plants, including crop plants with familiar traits, will complete the RSR process after the initial review, while others will require a PPRA. Whether a plant will complete the process after the initial review depends on the plant-trait-mechanism of action combination and we cannot speculate on the types of submissions we may receive.

The 2019 Plant Pest Risk Assessment (PPRA) Framework document mentioned the use of a Plant Reference Document (PRD) to support problem formulation. In the Regulatory Status Review (RSR) guidance, the role of these documents is not mentioned. Can you clarify the need for and use of the PRD in the RSR process?
The guidance discusses that plausible pathways to increased plant pest risk are based on the biology of the plant and the mechanism of action imparted and the trait. The PRD is an internal APHIS document where we review scientific information on the biology and impacts of a plant species. It is a foundational tool used for the initial review.

As regards the bioinformatics methods used to identify potential unintended edits in homologous sequences, does BRS recommend particular methods to requesters or use them for their own analysis?
BRS does not recommend particular methods that should be used to examine whether there are unintended edits in homologous sequences. Whatever method is used should be sufficiently reliable to justify the conclusions.

In considering plant pest risk, how much weight does APHIS give the physical chemistry of herbicides used in herbicide-resistant cultivars that may drift or volatilize and affect other non-resistant plants? Example: the dicamba-resistant soybean fiasco
The Regulatory Status Review considers that plant pest risk associated with the modified plant. Issues related to herbicide use and labeling are considered by the Environmental Protection Agency under their pesticide regulations.

Given the panelist's response to the question about providing Tier 1 safety data for an insect plant in the original Regulatory Status Review submission, I believe that BRS needs to reconsider its position. Ignoring data relevant to plausible plant pest risk in a submission seems scientifically indefensible.
The separation of problem formulation, setting the scope of the analysis, in the initial review, and the analysis of plausible pathways to increased plant pest risk in the Plant Pest Risk Assessment (PPRA) does not ignore relevant data. It is meant to separate the scoping and analysis processes. The initial review does not accommodate analysis of risk data because of the way the process is set up and because it does not include steps the Agency needs to perform when analyzing data, such as a public comment period for the draft PPRA.

Page 15 of the draft Regulatory Status Review (RSR) Guide says "...anyone may request ..." a re-review. What process will BRS use if this re-review requestor is not the initial requestor, e.g., a potential competitor or another applicant?
After an RSR, anyone may request that APHIS re-review its finding provided such a request provides new, scientifically valid evidence bearing on the plant pest risk associated with movement of the plant.

How can I learn about trade outside of the U.S.? Should developers have concerns about the distribution of exempt plants?
BRS does not have any regulatory authority over trade. The U.S. Trade Representative's Office of Agricultural Affairs has overall responsibility for U.S. government trade negotiations and policy development and coordination regarding agriculture, including agricultural regulatory issues (e.g., biotechnology, cloning, etc.).

When the genetic elements in the insertion have too many differences with known sequences (with accession #), would you prefer us to prepare the table with the intended insertion instead of the real inserted material?
The submission should include the exact sequence inserted or intended to be inserted. Identification or accession numbers are needed only when there is an appropriate number for

the genetic element. If there are a few differences, the requester could give the accession number and explain the differences between the inserted sequence and the one corresponding to the accession number. If the differences are so great that the accession number is not relevant to the inserted sequence, then the accession number need not be included.