**USDA-APHIS Biotechnology Regulatory Services**

# Request to Extend Nonregulated Status from a Previous Determination: Extension Guidance for Developers

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Biotechnology Regulatory Services
Animal and Plant Health Inspection Service
United States Department of Agriculture

4700 River Road
Riverdale, MD 20737

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## Introduction to the Extension Process

The Animal and Plant Health Inspection Service (APHIS) of the U.S. Department of Agriculture (USDA) has the responsibility, under the Plant Protection Act of 2000, to prevent the introduction and dissemination into the United States or interstate of plant pests. Under this authority, APHIS has published regulations found at 7 CFR part 340 pertaining to the introduction (importation, interstate movement, and release into the environment) of genetically engineered (GE) organisms and products derived from known plant pests (regulated articles). Before introducing a regulated article, a person is required under §340.0 of the regulations to either: (1) notify APHIS and receive an acknowledgement in accordance with §340.3 or (2) obtain a permit in accordance with §340.4. An organism is not subject to the regulations if it is determined that it is not a plant pest or after a thorough evaluation, the agency determines that it does not present a plant pest risk. The regulations at §340.6 entitled "Petition for determination of nonregulated status," provide that a person may petition APHIS to evaluate submitted data requesting that APHIS determine that a regulated article is unlikely to pose a plant pest risk and will no longer be regulated. If APHIS determines that the regulated article does not present a risk of introduction or dissemination of a plant pest, the petition will be granted, thereby allowing unrestricted introduction of the article.

In addition, §340.6(e) of the regulations provides that APHIS may extend a determination of nonregulated status to other regulated articles upon finding that these regulated articles are sufficiently similar to one or more articles that have been granted nonregulated status because they do not present a risk of introduction or dissemination of a plant pest . Such a finding would be made based on an evaluation of the similarity of the regulated articles to antecedent organism(s), *i.e.*, an organism(s) that has already been the subject of a determination of nonregulated status by APHIS under §340.6, and that is used as a reference for comparison to the regulated article(s) under consideration.

For actions such as determinations of nonregulated status and extensions of nonregulated status, APHIS prepares environmental documentation as part of its obligations under the National Environmental Policy Act (NEPA) of 1969 and the APHIS NEPA implementing regulations at 7 CFR part 372. Whenever possible, APHIS will use existing Environmental Assessments (EAs) or Environmental Impact Statements (EISs) for the antecedent organism(s). In some cases, only new Findings of No Significant Impact (FONSIs) will be required. In other cases, new EAs will be written to update relevant information from previous environmental documents and/or to combine the analysis from multiple environmental documents when there are multiple antecedents.

APHIS is providing the following guidance to help a person determine whether and how to prepare a request for an extension of a determination of nonregulated status. We recommend discussing your request for extension of nonregulated status with APHIS prior to submission.

## Extension Eligibility Considerations

The aim of making comparisons between regulated articles for which a person is seeking an extension of a determination of nonregulated status and antecedent organisms is to ensure that

the regulated articles under consideration are unlikely to pose plant pest risks beyond those considered in the initial determination of nonregulated status.

## *Functional Equivalency Considerations*

In evaluating the similarity between two GE plants, APHIS considers whether the mechanisms-of-action of the introduced traits are functionally equivalent. For example, one mechanism-of-action for resistance in plants to the herbicide glyphosate relies on an inability of glyphosate molecules to bind and inactivate an enzyme called EPSPS, which is responsible for an essential step in a biochemical pathway for the synthesis of certain amino acids. If glyphosate cannot bind to the EPSPS enzyme, the plant is resistant to the herbicide. APHIS has granted nonregulated status to two very similar types of GE plants which differed in the donor organism for the *epsps* genes: one version of the gene was derived from corn (*mepsps*) and the other from a strain of *Agrobacterium* (*CP4 epsps*). In both cases the added gene encodes an EPSPS protein which does not bind to glyphosate. These two glyphosate resistance traits have mechanisms-of-action which are functionally equivalent, so either should be a suitable antecedent for the other.

Glyphosate resistance can also be accomplished by other mechanisms-of-action. For example, the protein glyphosate acetyl transferase (GAT) gives resistance by metabolizing glyphosate to an inactive form. Therefore, glyphosate resistance accomplished through GAT is not functionally equivalent to glyphosate resistance achieved by an added *epsps* gene. Therefore, a glyphosate-resistant corn that uses a *gat* gene to achieve glyphosate resistance is not similar enough to be used as an antecedent for a glyphosate-resistant corn developed by adding an *epsps* gene.

## *Crop Considerations*

In addition to considering the mechanism-of-action of a particular trait, APHIS also considers the crop in which the trait is expressed. For instance, if APHIS had never reviewed an herbicide-resistant soybean before, soybean transformed with an *epsps* gene (*mepsps* or *cp4*) would not be eligible for an extension based on an antecedent corn variety transformed with an *epsps* gene (i.e., the previously reviewed crop). However, if another herbicide-resistant soybean had been previously reviewed with a different herbicide resistance, such as a glufosinate-resistant soybean, APHIS would evaluate whether the extension process was appropriate for an EPSPS soybean based on two antecedents, the glufosinate-resistant soybean which has the same phenotype category (herbicide-resistance) and the EPSPS corn which has a functionally equivalent mechanism-of-action. Whether the extension process would be used would depend on the extent to which the agency identifies additional issues not previously addressed in the two prior reviews.

Thus, to be considered for the extension process, 1) APHIS must have made a prior determination of nonregulated status of the mechanism-of-action for the trait of interest in any crop, and 2) APHIS must have made a determination of nonregulated status for the phenotype category (e.g. herbicide resistance, insect resistance) in the subject crop.

APHIS anticipates the extension process being applicable in the following cases:

1) Where a previously reviewed trait is introduced into different varieties of the same crop. For example, various apple varieties genetically engineered with the same non-browning trait as in one of the antecedent Arctic® apple events in 'Golden Delicious' and 'Granny Smith' varieties (10-161-01p).

2) Where traits previously reviewed separately in a particular crop are stacked into the same crop by introducing them together through genetic engineering. For example, a stacked corn line is created by introducing both a *mepsps* gene (previously reviewed in corn) and a *cry* gene from *Bacillus thuringiensis* (previously reviewed in corn). In this case there will be two or more antecedents.

3) Where phenotype categories have been reviewed previously in the crop but a mechanism-of-action new to the crop has been reviewed in another crop. For example, if the *hppd* gene, which confers resistance to mesotrione herbicide, is introduced in corn (*hppd* was previously reviewed in soybean and many herbicide-resistant corn lines have been reviewed). In this case there will be two or more antecedents.

While the three cases are eligible for the extension process, the similarity of the product being considered for an extension (potential extension) to the antecedents decreases from case 1 to case 3. Consequently the timelines for review may become longer as the degree of similarity decreases. There may be instances in case 3 where issues are different enough between the potential extension and the antecedent organism(s) that APHIS determines that the extension process is not appropriate and the petition process should be used. Also, because the potential extension is somewhat different, previous NEPA analyses may not be sufficient and additional analyses may be required. Nevertheless, APHIS believes that most products that meet one of the three criteria are likely to qualify for the extension process, and that the review will be completed within eight months after receiving a complete dossier.

## Request for Extension of a Previous Determination of Nonregulated Status

For APHIS to grant an extension of a determination of nonregulated status to other regulated articles, the agency must determine that the new regulated articles in question raise no new issues meriting separate review under the petition process. Including the following information in the submitter's dossier will facilitate APHIS' review of extension request:

- A complete description of the genotype and phenotype of the regulated article(s). This includes a description of the following:
    - Genetic modifications in the regulated article(s) under consideration.
    - Function and donor organisms for any inserted genetic material.
    - Transformation vector.
    - Mechanism-of-action of the genetic modification.

- Compositional analysis (not typically required but may be requested) when the trait may be expected to cause changes to metabolites or compounds which could affect the plant pest risk.

- A molecular characterization of the regulated article.

- A complete, concise, written narrative comparison and summary table of the antecedent organism(s) and the regulated article. This characterization may demonstrate that the modifications in the regulated articles are of one or more of the types illustrated in the eligibility considerations discussed above.

- Information on the phenotypic expression of the genetic modifications in the regulated article(s) and any known differences in phenotype between the regulated article(s) and their antecedent organism(s). These known differences should be further categorized as to whether they are expected based on the intended effect of the new modifications.

- The petition number(s) of the determinations from which this extension is requested.