c e r e s

July 23, 2012

Mr. Michael Gregoire
Deputy Administrator
Biotechnology Regulatory Services
Animal and Plant Health Inspection Service
United States Department of Agriculture
4700 River Road, Unit 98
Riverdale, MD 20737

Re: Confirmation that TRG101W Transgenic Switchgrass is not a regulated article

Dear Mr. Gregoire,

Ceres, Inc. (Ceres) is developing technology that will enable dedicated energy crops to be more productive and efficient in their use as feedstocks for the advanced biofuels and biopower industries. One of the products that Ceres is focused on is genetically modified switchgrass (*Panicum virgatum* L.) ("TRG101W Transgenic Switchgrass"). TRG101W Transgenic Switchgrass has enhanced water use efficiency. Switchgrass will likely be grown under rain fed conditions making it susceptible to reduced yields during periods of drought. Thus, improving water use efficiency is not only critical for successful establishment and productivity of switchgrass, but it also provides an economical and environmentally favorable solution.

Because switchgrass is not a plant pest or an invasive species, the genetic elements used to generate TRG101W Transgenic Switchgrass are all sourced from fully classified organisms, and the transformation process does not introduce any plant pest DNA components, there is no scientifically valid basis for concluding that TRG101W Transgenic Switchgrass is, or will become, a plant pest within the meaning of the Plant Protection Act (PPA)[1]. Ceres therefore asserts that under current regulations, TRG101W Transgenic Switchgrass is not a regulated article within the meaning of 7 CFR §340.1 because it does not satisfy any of the regulatory criteria that would subject it to the oversight of the USDA's Animal Plant Health and Inspection Service (APHIS).

Before proceeding further with product development, Ceres requests that APHIS confirm that TRG101W Transgenic Switchgrass, modified without any plant pest elements (as described more fully in Table 1 below), should not be considered a regulated article within the meaning of

[1] Plant Protection Act; 7 U.S.C. §7701, et seq. (2000)

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the current regulations. If the agency does not concur with Ceres' interpretation of the current regulations, Ceres requests that the Agency provides Ceres with its scientific rationale for concluding that TRG101W Transgenic Switchgrass is or will become a plant pest.

I. Transformation Background.

To further assist APHIS in understanding the origin of TRG101W Transgenic Switchgrass, a summary of information on the recipient plant, as well as the genetic and technical elements used to modify the recipient plant to make TRG101W Transgenic Switchgrass, is provided below.

A. TRG101W Transgenic Switchgrass (*Panicum virgatum* L.)

Transformation of switchgrass, using purified DNA that is transferred by biolistic (gene gun) methods, results in stably integrated DNA. DNA transfer does not involve *Agrobacterium* transformation or any other plant pest that is currently regulated under the PPA. Using the genetic elements described in Table 1, the genetically enhanced materials express the TRG101W trait, which causes better water use efficiency resulting in a higher yielding switchgrass crop. Table 1 below describes each genetic element and identifies its respective sources and functions.

B. Recipient Switchgrass (*Panicum virgatum* L.)

Switchgrass is not a federal noxious weed.[2] It is a native and dominant species of the central North American tall grass prairie and is listed as an agricultural seed (7 CFR §361). It is commonly found in pastures, along roadsides and is used primarily for soil conservation, forage production and as an ornamental grass[3]. More recently it has been used as a biomass crop for biofuel production. Switchgrass is a warm-season perennial grass typically found south of latitude 55° N across North America.

[2] http://plants.usda.gov/java/invasiveOne?startChar=P
[3] http://www.ernstseed.com/seed-mix/species/?catalog-id=244

Table 1. Genetic Elements in TRG101W Commercial Construct for Biolistic Transformation of Switchgrass.

GENETIC ELEMENT	SOURCE	FUNCTION
MCS	*Synthetic*	Multicloning site (MCS) allows easy insertion of DNA fragment
Term5	*Arabidopsis thaliana*	Transcription terminator for TRG101W gene
TRG101W	*Hordeum vulgare*	TRG101W gene encoding a protein affecting water use
pBE2	*Oryza sativa*	Promoter to regulate the transcription of TRG101W gene
Term5	*Arabidopsis thaliana*	Transcription terminator for NPT II gene
NPT II	*Escherichia coli* K-12	Gene encoding neomycin phosphotransferase II (NPT II)
pCS1	*Arabidopsis thaliana*	Promoter to regulate the transcription of NPT II gene
MCS	*Synthetic*	Multicloning site allows easy insertion of DNA fragment

II. APHIS' Interpretation of Its 7 CFR §340 Regulation Dictates a Finding that TRG101B Transgenic Switchgrass is Not a Regulated Article

A. APHIS Has Been Clear That Not All Transgenic Plants Are Subject to Regulatory Oversight

APHIS defines a "regulated article" as (Part 340.1):

> Any organism which has been altered or produced through genetic engineering, if the donor organism, recipient organism, or vector or vector agent belongs to any genera or taxa designated in §340.2 and meets the definition of plant pest, or is an unclassified organism and/or an organism whose classification is unknown, or any product which contains such an organism, or any other organism or product altered or produced through genetic engineering which the Administrator, determines is a plant pest or has reason to believe is a plant pest. Excluded are recipient microorganisms which are not plant pests and which have resulted from the addition of genetic material from a donor organism where the material is well characterized and contains only non-coding regulatory regions.[4]

Consistent with the PPA's definition of a plant pest, APHIS further defines a "plant pest" as:

> *Plant pest.* Any living stage (including active and dormant forms) of insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi, other parasitic plants or reproductive parts thereof; viruses; or any organisms similar to or allied with any of the foregoing; or any infectious agents or substances, which can directly or indirectly injure or cause disease or damage in or to any plants or parts thereof, or any processed, manufactured, or other products of plants.[5]

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[4] *Well-characterized and contains only non-coding regulatory regions* (*e.g.*, operators, promoters, origins of replication, terminators, and ribosome binding regions). The genetic material added to a microorganism in which the following can be documented about such genetic material: (a) The exact nucleotide base sequence of the regulatory region and any inserted flanking nucleotides; (b) The regulatory region and any inserted flanking nucleotides do not code for protein or peptide; and (c) The regulatory region solely controls the activity of other sequences that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis. (7 CFR §340.1).

[5] 7 CFR §340.1

APHIS further claims that its regulations are consistent with the Coordinated Framework, because they apply "only [to] genetically engineered organisms or products which are plant pests or for which there is a reason to believe are plant pests, and not to…an organism or product merely because of the process by which it was produced."[6] APHIS has further stated that its concern arises only "when an organism or product is altered or produced by genetic engineering and one or more of its constituents (donor, vector/vector agent or recipient) comes from a family or genus of organisms known to contain plant pests…. This is because… there is a risk that certain undesirable traits may be transferred to the new organism and may survive when the organism is released into the environment."[7]

APHIS reiterated this policy on several occasions, first when it introduced its notification and permit process for the confined release of transgenic organisms,[8] and again during the proposed revision to its regulations.[9] It has been clear that not all transgenic plants are to be regulated, and those that are belong to the limited group of "plant pests" as defined in the regulations.

B. TRG101W Transgenic Switchgrass Does Not Fall Within the Regulatory Definition of a "Regulated Article."

Under APHIS regulations, a transgenic organism is considered a "regulated article" "if the donor organism, recipient organism, or vector agent(s) belongs to a genera or taxa designated in 7 CFR §340.2, *and* the organism meets the definition of a plant pest (emphasis added)." The language of the regulation requires that both criteria must be met to satisfy the definition of a regulated article.

For TRG101W Transgenic Switchgrass, none of the donor organisms, the recipient organism, or the vectors Ceres will utilize to transform switchgrass

[6] 51 Fed. Reg. 23352 (proposed rule); 52 Fed.Reg. 22892 (final rule where similar language is used).
[7] Office of Science and Technology Policy's Coordinated Framework for Regulation of Biotechnology, June 26, 1986 (51 Fed.Reg. 23302).
[8] 57 Fed. Reg. 53036 (Feb 1991)
[9] 73 Fed. Reg. 60008, 60010 (Oct 8, 2008)

belong to any taxa identified in §340.2. Further, none of the genetic elements described in Table 1 are sourced from any plant pest. In addition, the recipient organism, switchgrass, is not a plant pest. Therefore, TRG101W Transgenic Switchgrass using the genetic elements identified in Table 1 does not satisfy either of the criteria set forth to qualify as a "regulated article."

Another definition of a "regulated article" includes transgenic organisms that are unclassified or whose classification is unknown. Other types of organisms that could raise concerns are "pathogens, predators or parasites of natural enemies of plant pests or weeds or of commercially available pollinators such as honeybees, bumble bees and alkali bees."[10] However, since the introduced trait enhances water efficiency, it does not change the plants' basic biological characteristics and the trait's presence does not produce a plant that would directly feed on, infect, parasitize, or contaminate plants, or adversely affect other organisms that are beneficial to plants.

III. Finding that TRG101W Transgenic Switchgrass is Not a Regulated Article is Consistent With Previous APHIS Determinations and Also Applies to Stacks of Other Products that are Not "Regulated Articles."

APHIS has made a number of different determinations that transgenic plants are not "regulated articles," including TRG101B Transgenic Switchgrass, as described in a letter to CERES (dated April 24, 2012). TRG101B Transgenic Switchgrass produces greater biomass and contains more fermentable sugars than conventional switchgrass varieties, thereby offering a higher yield potential. Several other examples are also posted on USDA's website.[11]

CERES would also appreciate confirmation from APHIS that any transgene stacks, produced through molecular or breeding techniques, with other products deemed as not regulated articles, or have been granted de-regulated status, would also have the same designation, not "regulated articles" under 7 CFR §340. Such a designation of stacks such as for those under development at CERES, all of which are combinations of what would be determined as not "regulated articles," would allow CERES flexibility to commercialize products with improved characteristics as feedstocks for the advanced biofuels and biopower industries.

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[10] 66 Fed. Reg. 51340 (Oct 9, 2001)
[11] http://www.aphis.usda.gov/biotechnology/reg_loi.shtml

IV. Summary of Conclusions

In summary, switchgrass is not itself a plant pest, there are no plant pest elements involved in the production of TRG101W Transgenic Switchgrass, and all the native genomes that are sources for the genetic elements that will be used have been fully classified. Therefore, there is no scientifically valid basis to determine that TRG101W Transgenic Switchgrass is or will become a plant pest within the meaning of the PPA. Likewise, a stack of any other event deemed not a "regulated article" or previously deregulated, with TRG101W Transgenic Switchgrass would result in a product that is not a "regulated article."

We look forward to receiving your response, and thank you in advance for your consideration and prompt confirmation of Ceres' position that TRG101W Transgenic Switchgrass is not a "regulated article" for the reasons described herein.

Sincerely,

Richard Hamilton
President and Chief Executive Officer

cc: Honorable Tom Vilsack, Secretary of U.S. Department of Agriculture

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Re: Confidential Business Information ("CBI") Claim Justification regarding TRG101W Transgenic Switchgrass

Dear Mr. Gregoire,

THE FOLLOWING CONTAINS CONFIDENTIAL BUSINESS INFORMATION

In support of the letter of inquiry dated July 23, 2012, from Ceres, Inc. (Ceres) to you requesting confirmation that TRG101W Transgenic Switchgrass is not a regulated article, attached are hard copies of two published articles (the "Literature") that refer to a gene that is a homolog of a gene referred to in Ceres' letter of inquiry.

Ceres respectfully requests that the Literature be designated and handled as CBI pursuant to the Trade Secrets Act (18 U.S.C. § 1905), the Freedom of Information Act, 5 U.S.C. § 552(b)(4), and APHIS' policy statement published in the Federal Register, 50 FR 38561, September 23, 1985 concerning documents that contain CBI relating to biotechnology. Ceres' justification for this request is as follows:

The Literature qualifies as CBI in this context because the very fact that Ceres is submitting the Literature in connection with and in support of its letter of inquiry, constitutes a trade secret of Ceres. A trade secret is information relating to a production process, including without limitation processes and research methodology, that is not publicly known and that can cause economic harm if competitors obtain it. Disclosure of the link between the Literature and Ceres' letter of inquiry would enable a third party to draw an inference that the gene referred to

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in the Literature was homologous to the Ceres gene referred to in its letter of inquiry. Revealing this trade secret would be sufficient to cause competitive harm inasmuch as it would alert third parties, including competitors, to the utility of the specific gene identified in the Literature to confer the desired traits in the crops of commercial interest to Ceres. The link between the Literature and the Ceres letter of inquiry is commercially valuable and release of the fact of such connection, in this context, would cause substantial competitive harm and irreparable damage to Ceres.

Currently, the commercial application of the gene referred to in the Literature into Ceres' commercial crops is not common knowledge. Since the Ceres product that is the subject of our letter of inquiry has not yet been commercialized, we are using the Literature in our business and maintaining the information contained in the Literature, as it relates to our business, in secrecy as a trade secret. Release of the fact that the Literature was provided by Ceres in support of its letter of inquiry would disclose this trade secret, and could enable Ceres' competitors to engineer similar products that circumvent Ceres' intellectual property protection. Accordingly, the Literature should be designated as CBI and the fact of its submission in this context should not be disclosed.

Thank you very much for your consideration. Should you have any questions, please feel free to call at your convenience.

Sincerely,

Richard Hamilton
President and Chief Executive Officer