c e r e s

February 22, 2013

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 TRSBG101B Transgenic Sorghum 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 domesticated sorghum (*Sorghum bicolor* (L.) Moench *ssp. bicolor*) ("TRSBG101B Transgenic Sorghum"). TRSBG101B Transgenic Sorghum produces greater biomass and contains more fermentable sugars than non-genetically modified sorghum checks, thereby offering a higher yield potential.

Because domesticated sorghum is not a plant pest or listed as a federal noxious weed[1], the genetic elements used to generate TRSBG101B Transgenic Sorghum 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 TRSBG101B Transgenic Sorghum is, or will become, a plant pest within the meaning of the Plant Protection Act (PPA)[2]. Ceres therefore asserts that under current regulations, TRSBG101B Transgenic Sorghum 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 TRSBG101B Transgenic Sorghum, 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 the current regulations. If the agency does not concur with Ceres' interpretation of the current

[1] http://plants.usda.gov/java/noxious
[2] Plant Protection Act; 7 U.S.C. §7701, et seq. (2000)

regulations, Ceres requests that the Agency provides Ceres with its scientific rationale for concluding that TRSBG101B Transgenic Sorghum is, or will become a plant pest.

I. Transformation Background.

To further assist APHIS in understanding the origin of TRSBG101B Transgenic Sorghum, a summary of information on the recipient plant, as well as the genetic and technical elements used to modify the recipient plant to make TRSBG101B Transgenic Sorghum, is provided below.

A. TRSBG101B Transgenic Sorghum (*Sorghum bicolor* (L.) Moench *ssp. bicolor*)

Transformation of sorghum, 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 TRSBG101B trait, which causes the growth of more biomass and the formation of more fermentable sugars, resulting in a higher yielding sorghum crop. Table 1 below describes each genetic element and identifies its respective sources and functions.

B. Recipient Sorghum (*Sorghum bicolor* (L.) Moench *ssp. bicolor*)

Historically, domesticated sorghums have been used for grain, forage, or sugar crops. In the U.S. sorghum grain is primarily used for livestock feed and in a growing number of ethanol plants. Sweet varieties of sorghum are being used as a bioenergy crop for biofuel production where it has many desirable qualities. It has a high concentration of soluble sugars in the juice and achieves substantial biomass and fermentable sugar yield with minimal fertilizer and water inputs. It can be grown as a seeded annual, and can realize maximum sugar yield in a single short growing season across a wide geographic area within the US. Sweet sorghum juice contains an average of 15-23% (w/w) total fermentable sugars[3] including sucrose, fructose, and glucose, which can be

[3] http://www.swcs.org/documents/resources/Chapter_9__Shoemaker__Sorghum_C07AF2168027B.pdf

readily used for bioethanol production. Domesticated sorghum is a widely adaptable crop native to tropical and subtropical regions and is cultivated in warm climates worldwide.

Table 1. Genetic Elements in TRSBG101B Commercial Construct for Biolistic Transformation of Sorghum.

GENETIC ELEMENT	SOURCE	FUNCTION
MCS	*Synthetic*	Multicloning site allows easy insertion of DNA fragments
Term5	*Arabidopsis thaliana*	Transcription terminator for the TRSBG101B gene
TRSBG101B	*Sorghum bicolor*	TRSBG101B gene encodes a protein affecting plant growth and fermentable sugar accumulation
pBE5	*Sorghum bicolor*	Promoter to regulate the transcription of the TRSBG101B gene
Term5	*Arabidopsis thaliana*	Transcription terminator for the neomycin phosphotransferase II (NPT II) gene
NPT II	*Escherichia coli* K-12	Gene encoding NPT II
pCS1	*Arabidopsis thaliana*	Promoter to regulate the transcription of NPT II
MCS	*Synthetic*	Multicloning site allows easy insertion of DNA fragments

c e r e s

II. APHIS' Interpretation of Its 7 CFR §340 Regulation Dictates a Finding that TRSBG101B Transgenic Sorghum 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]

[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

c e r e s

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. TRSBG101B Transgenic Sorghum 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 TRSBG101B Transgenic Sorghum, none of the donor organisms, the recipient organism, or the vectors Ceres will utilize to transform sorghum belong

[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)

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, domesticated sorghum, is not a plant pest. Therefore, TRSBG101B Transgenic Sorghum 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 biomass, 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 TRSBG101B Transgenic Sorghum 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.

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

c e r e s

IV. Summary of Conclusions

In summary, domesticated sorghum is not itself a plant pest, there are no plant pest elements involved in the production of TRSBG101B Transgenic Sorghum, 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 TRSBG101B Transgenic Sorghum 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 TRSBG101B Transgenic Sorghum 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 TRSBG101B Transgenic Sorghum 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

Ceres, Inc. ~ 1535 Rancho Conejo Blvd. ~ Thousand Oaks, CA 91320
tel +1 (805) 376 6500 ~ fax +1 (805) 498 1002