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August 30, 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 Biolistically-derived GE Maize is not a Regulated Article

This document contains Confidential Business Information

A redacted version of this document is included herewith

Dear Mr. Gregoire,

Ceres, Inc. ("Ceres") has developed and/or identified GE trait technology that we wish to transform into maize (*Zea mays*). The genetic elements comprising our GE traits consist of promoters, coding sequences, and UTRs that are derived from plants or other fully classified organisms that are not considered plant pests. Our intended method of introducing these traits into maize is through use of biolistics, or "gene-gun," approach, which does not require the use of *Agrobacterium or Agrobacterium*-derived DNA sequences. Our target organism, maize, is not considered a plant pest or invasive species. Henceforth, this combination of methods and elements shall be referred to as Biolistically-derived GE Maize.

Because maize is not a plant pest or an invasive species, the genetic elements we will use to generate transgenic maize 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 our Biolistically-derived GE Maize will become a plant pest within the meaning of the Plant Protection Act (PPA)[1]. Ceres therefore asserts that under current regulations, Biolistically-derived GE Maize 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).

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

Before proceeding further with product development, Ceres requests that APHIS confirm that our intended Biolistically-derived GE Maize (as described more fully in Section I 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 regulations, Ceres requests that the Agency provides Ceres with its scientific rationale for concluding that our approach to Biolistically-derived GE Maize is subject to regulation.

I. Transformation Background.

To further assist APHIS in understanding the origin of Biolistically-derived GE Maize, a summary of information on the recipient plant, as well as the genetic and technical elements used to modify the recipient plant to make these events, is provided below.

A. Recipient Organism (*Zea mays*)

Zea mays (also known as maize or corn) is a monocot grass species cultivated throughout much of the world for use as a food and feed crop. In a letter to Dow AgroScience LLC, dated May 26th, 2010, your office issued a public comment that maize is not considered a plant pest[2] saying that "There is no reason to believe that *Zea mays* containing an IPK1 deletion is a plant pest or is likely to pose a plant pest risk."

B. Transformation Method

Biolistic transformation of maize does not involve *Agrobacterium* transformation or any other plant pest that is currently regulated under the PPA. We intend to use this transformation method to stably integrate linearized DNA that is purified from all vector backbone sequences.

C. Genetic Elements

Table 1 below describes each genetic element and identifies its respective sources and functions.

[2] http://www.aphis.usda.gov/biotechnology/reg_loi.shtml

Table 1. Genetic Elements for Biolistic Transformation of Maize.

GENETIC ELEMENTS	SOURCE	FUNCTION
MCS	*Synthetic*	Multiple Cloning Site: Cleavage site for multiple restriction endonucleases - enables cleavage of linear DNA fragments from cloning vector. A MCS will appear on both ends of the linear DNA fragment that is being introduced into the plant.
Promoter elements		
pBE01	Arabidopsis	
pBE05	*Sorghum bicolor*	
pRT01	*Sorghum bicolor*	
pDI2	Arabidopsis	
pBE10	*Oryza sativa*	
pCS1	Arabidopsis	
Trait Genes		
	Zea mays	Improved digestibility
	Zea mays	Improved digestibility
	Bacillus thuringiensis	Plant protectant with insecticidal properties
	Panicum virgatum	Improved palatability
	Populus trichocarpa	Drought tolerance
	Panicum virgatum	Drought tolerance
	Panicum virgatum	Increased seed yield and dwarfing
	Arabidopsis	Increased seed yield and dwarfing
NPT II	*Escherichia coli* K-12	Gene encoding NPT II for tissue culture selection
3' UTR Elements		
Term2	Arabidopsis	Transcription terminator for the Trait gene of interest
Term3	Arabidopsis	Transcription terminator for the Trait gene of interest
Term5	Arabidopsis	Transcription terminator for neomycin phosphotransferase II (NPT II)

II. APHIS' Interpretation of Its 7 CFR §340 Regulation Dictates a Finding that Biolistic Transformation of Maize with Non-plant Pest Sequences Are Not Regulated Articles

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.[3]

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

[3] *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).

indirectly injure or cause disease or damage in or to any plants or parts thereof, or any processed, manufactured, or other products of plants.[4]

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."[5] 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."[6]

APHIS reiterated this policy on several occasions, first when it introduced its notification and permit process for the confined release of transgenic organisms,[7] and again during the proposed revision to its regulations.[8] 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. Biolistic Transformation of Maize with Non-plant Pest Sequences 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

[4] 7 CFR §340.1
[5] 51 Fed. Reg. 23352 (proposed rule); 52 Fed.Reg. 22892 (final rule where similar language is used).
[6] Office of Science and Technology Policy's Coordinated Framework for Regulation of Biotechnology, June 26, 1986 (51 Fed.Reg. 23302).
[7] 57 Fed. Reg. 53036 (Feb 1991)
[8] 73 Fed. Reg. 60008, 60010 (Oct 8, 2008)

requires that both criteria must be met to satisfy the definition of a regulated article.

For the purpose of the GE Biolistic transformation of maize described herein, none of the donor organisms, the recipient organism, or the vectors Ceres will utilize to transform maize 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, maize, is not a plant pest. Therefore, biolistically transformed maize 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."[9] The introduced traits described in Table 1 do 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 Biolistically-Derived GE Maize is Not-Regulated Also Applies to Stacks Created by Combining With Other Products that are Not "Regulated Articles."

Ceres would also appreciate confirmation from APHIS that any transgene stacks, produced through molecular or breeding techniques, of Biolistically-derived GE Maize 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 article", would allow Ceres flexibility to commercialize products with improved characteristics.

[9] 66 Fed. Reg. 51340 (Oct 9, 2001)

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IV. Summary of Conclusions

In summary, maize is not itself a plant pest, there are no plant pest elements involved in the production of biolistically derived GE maize, 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 the GE organism described herein 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 an event produced by such means 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 Biolistically-derived GE maize 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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