

Biotechnology Notification File No. 000200 CVM Note to the File

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To: Administrative Record, BNF No. 000200

Subject: Event COR23134 Soybean

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Purpose

This document summarizes the Food and Drug Administration (FDA) Center for Veterinary Medicine's (CVM, we) evaluation of biotechnology notification file (BNF) number 000200. Pioneer Hi-Bred International, Inc. (Pioneer) submitted a safety and nutritional assessment for a genetically engineered (GE) soybean, transformation event COR-23134-4 (hereafter referred to as COR23134 soybean), and additional information afterwards. We evaluated the information in Pioneer's submissions to ensure that regulatory and safety issues regarding animal food derived from COR23134 soybean have been resolved prior to commercial distribution. FDA's Human Foods Program summarizes its evaluation of uses of COR23134 soybean in human food in a separate document.

In CVM's evaluation, we considered all of the information provided by Pioneer as well as publicly available information and information in the agency's files. Here we discuss the outcome of the consultation for animal food use, but do not intend to restate the information provided in the final consultation in its entirety.

Intended Effects

The intended effect of the modifications in COR23134 soybean is to provide resistance to certain susceptible lepidopteran pests. To confer the insect resistance trait, Pioneer introduced three resistance genes: *cry1B.34.1* and *cry1B.61.1* gene from *Bacillus thuringiensis*, *ipd083Cb* gene from *Adiantum trapeziforme* var. *braziliense*, which confer protection against certain lepidopteran pests. Pioneer also introduced the *gm-hra_1* gene from soybean that encodes the *Glycine max* herbicide-resistant acetolactate

synthase (GM-HRA) protein which confers tolerance to the acetolactate synthase (ALS)-inhibiting herbicides and was used as a selectable marker.

Regulatory Considerations

The purpose of this evaluation is to determine whether use of the new plant variety in animal food raises safety or regulatory issues under the Federal Food, Drug and Cosmetic Act (FD&C Act).

The Environmental Protection Agency (EPA) defines a plant-incorporated protectant (PIP) as “a pesticidal substance that is intended to be produced and used in a living plant, or the produce thereof, and the genetic material necessary for the production of such a pesticidal substance,” including “any inert ingredient contained in the plant, or produce thereof” (40 CFR 174.3). EPA regulates PIPs under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the FD&C Act. Under EPA’s regulations, the Cry1B.34.1, Cry1B.61.1 and IPD083Cb proteins and the genetic materials used to express them in COR23134 soybean are considered pesticidal substances, and the GM-HRA protein and the genetic material used to express it in COR23134 soybean considered inert ingredients. Therefore, the safety assessment of these products falls under the regulatory purview of EPA.

Stability and Inheritance

Pioneer characterized the insertion event and stability of the inserted DNA in COR23134 soybean using Southern-by-Sequencing and junction sequence analysis. To confirm genomic stability, Pioneer performed southern blot on multiple breeding generations of COR23134 soybean. Pioneer states that there was a single site insertion of the T-DNA and that the inserted DNA was stably integrated into the genome across multiple generations of COR23134 soybean that were analyzed.

In addition, Pioneer assessed segregation of the inserted T-DNA using event specific polymerase chain reaction and herbicide tolerance phenotyping. The results of Chi-square analysis of the segregation data from multiple generations show that the segregation pattern of the inserted DNA is consistent with Mendelian principles of inheritance for a single locus. Pioneer concludes that the insert in COR23134 soybean was integrated at one locus and is stably transmitted across multiple generations in accordance with the principles of Mendelian inheritance.

Animal Food Use

Pioneer states that COR23134 soybean is expected to be grown for the same uses as currently commercialized soybean, and no new or specialty food or feed uses are anticipated. The typical uses of soybean-derived food and feed are well documented in Organisation for Economic Co-operation and Development (OECD) soybean composition consensus document¹. Most soybean seeds are processed into oil and meal. Soybean oil is commonly used as a human food ingredient. The preponderance of

¹ Organisation for Economic Co-operation and Development. 2012. Revised consensus document on compositional considerations for new varieties soybean [*Glycine max* (L.) Merr.]: Key food and feed nutrients, anti-nutrients, toxicants and allergens. Series on the Safety of Novel Foods and Feeds No. 25. ENV/JM/MONO 24. OECD, Paris

soybean meal is used in animal food, primarily in poultry, swine, and beef and dairy cattle diets. Soybean meal is processed in moist heat to inactivate trypsin inhibitors and lectins, which are anti-nutrients occurring in raw soybeans.

Composition

Scope of Analysis

Pioneer analyzed the nutrient composition of forage and grain obtained from COR23134 soybean, a non-GE near-isoline soybean variety (control), and four non-GE commercial soybean varieties (reference varieties)² at each site that were grown and harvested under similar conditions. The components selected for analyses were based on the OECD soybean composition consensus document.

Study Design

Pioneer conducted field trials in 2022 at eight sites in the United States and Canada. A randomized complete block design with four replicate plots at each field site was used. Pioneer harvested grain and forage from each replicate within each site for composition analysis. Forage samples were harvested at R3 growth stage and grain samples were harvested at R8 growth stage. Forage and grain samples were transported in chilled containers and then stored frozen until compositional analysis was performed.

Pioneer statistically compared each component for COR23134 soybean and the control across locations using a linear mixed model analysis of variance. Components were expressed on a dry matter basis, with the exception of fatty acids, prior to statistical analysis. Forage and grain moisture were not included in the statistical analyses. When a value for a component was less than the lower limit of quantification (LLOQ) for the analytical method, a value equal to half the LLOQ was assigned to this sample. For a given analyte in the mixed model analysis, if a statistical difference (P -value < 0.05) was observed between COR23134 soybean and the control soybean, the False Discovery Rate (FDR)-adjusted P -value was examined. Fisher's exact test was used if analytes did not meet criteria for enough observations above the LLOQ. Pioneer states that when a statistically significant difference was identified, the respective range of individual values from COR23134 soybean was compared to tolerance intervals ³. If the range of COR23134 soybean contained individual values outside the tolerance interval, it was then compared to the range of values in the public literature, including the Agriculture and Food Systems Institute Crop Composition Database. If the range of COR23134 soybean contained individual values outside the literature range, then these values were compared to the in-study reference range.

Results of Analyses

For forage, Pioneer reports values for proximates (moisture, crude protein, crude fat, carbohydrates by calculation, and ash) and fiber (crude fiber, acid detergent fiber (ADF)

² Pioneer reports 18 total reference soybean varieties.

³ Tolerance intervals are expected to contain at least 99% of the values for corresponding component of the conventional soybean population with a 95% confidence level from data obtained from non-GE soybean lines that were grown in commercial soybean-growing regions between 2005 and 2016 in the United States, Canada, Chile, Brazil, and Argentina. The combined data represent 81 commercial soybean lines and 175 unique environments.

and neutral detergent fiber (NDF)). Pioneer found no statistically significant differences between the mean values for these components in forage from COR23134 soybean and the control. Pioneer concludes that forage obtained from COR23134 soybean is comparable to forage from conventional soybean varieties.

For grain, Pioneer measured proximates, fiber (crude fiber, ADF and NDF), 18 amino acids, nine minerals, 23 fatty acids, eight vitamins, five antinutrients (phytic acid, raffinose, lectin, stachyose and trypsin inhibitor) and three isoflavones. Pioneer reports statistically significant differences between COR23134 soybean and the control in the levels of 23 components⁴. All of the individual values for these components fell within tolerance interval from conventional non-GE soybean lines, scientific literature range, and/or in-study reference range. Additionally, the FDR-adjusted P-values for 13 components were not statistically significant⁵. Pioneer concludes that the differences in these components between COR23134 soybean and the control are not biologically meaningful from an animal food safety perspective.

Summary of Compositional Analyses

Pioneer highlights that the genetic modification does not meaningfully affect nutrient composition and nutritional value of forage and grain derived from COR23134 soybean. Pioneer concludes that COR23134 soybean is comparable to soybean varieties that are currently used in animal food in the United States.

Conclusion

CVM evaluated Pioneer's submissions to determine whether COR23134 soybean raises any safety or regulatory issues with respect to its use in animal food. Based on the information provided by Pioneer and other information available to the agency, CVM did not identify any safety or regulatory issues under the FD&C Act that would require further evaluation at this time.

Pioneer concludes that COR23134 soybean and the animal foods derived from it are as safe as and are not materially different in composition or any other relevant parameter from other soybean varieties now grown, marketed, and consumed. At this time, based on Pioneer's data and information, CVM considers Pioneer's consultation on COR23134 soybean for use in animal food to be complete.

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⁴ These included crude protein, ash, carbohydrates, myristic acid, palmitic acid, heptadecanoic acid, heptadecenoic acid, linolenic acid, arginine, glutamic acid, glycine, isoleucine, leucine, proline, serine, valine, calcium, magnesium, phosphorus, vitamin B5, alpha - tocopherol, total daidzein equivalent, and total genistein equivalent.

⁵ These included ash, carbohydrates, linolenic acid, arginine, glycine, proline, serine, valine, magnesium, phosphorus, vitamin B5, alpha-tocopherol, and total daidzein equivalent.