

68467-6

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OCT 08 2008

Dr. Penny L. Hunst
Regulatory Leader - Biotech
Dow AgroSciences LLC
9330 Zionsville Road
Indianapolis, IN 46268

Dear Dr. Hunst:

Subject: Your March 18, 2008 Amendment Requests to Remove the Expiration Date and Amend the Insect Resistance Management Terms and Conditions for Herculex Xtra Insect Protection
EPA Registration No. 68467-6

The amendments referred to above, submitted in connection with registration under section 3(c)(7)(A) of the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, are acceptable subject to the following comments.

Expiration Date:

The subject registration will automatically expire on midnight September 30, 2010.

We are currently unaware of any issues that would preclude a decision to remove the expiration date in the future. However, due to other statutory priorities, BPPD's review of the data and information submitted as conditions of registration is ongoing. Therefore, the expiration date is being extended to match that of corn rootworm resistant Bt corn as an interim measure.

Insect Resistance Management:

The listed IRM terms and conditions are being modified as follows.

1) Under 5a. Refuge Requirements, the following statement is added "These refuge requirements do not apply to seed propagation of inbred and hybrid corn seed corn up to a total of 20,000 acres per county and up to a combined U.S. total of 250,000 acres per PIP active ingredient per registrant per year." Additionally, under the refuge location portion of subsection A. *Lepidopteran refuge for the CryIF component*, the phrases "(1/4 mile preferred)" and "(six preferred)" are deleted.

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2) Under 5d. Insect Resistance Monitoring and 5e. Remedial Action Plans, the Cry1F section is removed and replaced by the following. Additionally, the statement "A report on results of Cry1F resistance monitoring and investigations of damage reports must be submitted to the Agency annually by April 31st each year for the duration of the conditional registration." is being deleted.

5f. Cry1F Insect Resistance Monitoring

The Agency is imposing the following conditions for this product:

The registrant will monitor for resistance to its lepidopteran-resistant Bt corn. The monitoring program shall consist of two approaches: (1) focused population sampling and laboratory testing; and (2) investigation of reports of less-than expected control of labeled insects. Should field-relevant resistance be confirmed, an appropriate resistance management action plan will be implemented.

(1) Focused Population Sampling

The registrant shall annually sample and bioassay populations of the key target pests *Ostrinia nubilalis* (European corn borer; ECB), *Diatraea grandiosella* (Southwestern corn borer; SWCB), and *Helicoverpa zea* (corn earworm; CEW). Sampling for the target pests will be focused in areas identified as those with the highest risk of resistance development (e.g., where lepidopteran-active Bt hybrids are planted on a high proportion of the corn acres, and where the insect species are regarded as key pests of corn). Bioassay methods must be appropriate for the goal of detecting field-relevant shifts in population response to lepidopteran resistant Bt corn and/or changes in resistance allele frequency in response to the use of Bt corn and, as far as possible, should be consistent across sampling years to enable comparisons with historical data.

The number of populations to be collected shall reflect the regional importance of the insect species as a pest, and specific collection regions will be identified for each pest. For ECB, a minimum of 12 populations across the sampling region will be targeted for collection at each annual sampling. For SWCB, the target will be a minimum of six populations. For CEW, the target will be a minimum of 10 populations. Pest populations should be collected from multiple corn-growing states reflective of different geographies and agronomic conditions. To obtain sufficient sensitivity to detect resistance alleles before they become common enough to cause measurable field damage, each population collection shall attempt to target 400 insect genomes (egg masses, larvae, mated females, and/or mixed-sex adults), but a successful population collection will contain a minimum of 100 genomes. It is recognized that it may not be possible to collect the target number of insect populations or genomes due to factors such as natural fluctuations in pest density, environmental conditions, and area-wide pest suppression.

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The sampling program and geographic range of collections may be modified as appropriate based on changes in pest importance and for the adoption levels of lepidopteran-resistant Bt corn. The Agency shall be consulted prior to the implementation of such modifications.

The registrant will report to the Agency before August 31 each year the results of the population sampling and bioassay monitoring program.

Any incidence of unusually low sensitivity to the Bt protein in bioassays shall be investigated as soon as possible to understand any field relevance of such a finding. Such investigations shall proceed in a stepwise manner until the field relevance can be either confirmed or refuted, and results of these shall be reported to the Agency annually before August 31. The investigative steps will include:

1. Re-test progeny of the collected population to determine whether the unusual bioassay response is reproducible and heritable. If it is not reproducible and heritable, no further action is required.
2. If the unusual response is reproducible and heritable, progeny of insects that survive the diagnostic concentration will be tested using methods that are representative of exposure to Bt corn hybrids under field conditions. If progeny do not survive to adulthood, any suspected resistance is not field relevant and no further action is required.
3. If insects survive steps 1 and 2, resistance is confirmed, and further steps will be taken to evaluate the resistance. These steps may include:
 - determining the nature of the resistance (*i.e.*, recessive or dominant, and the level of functional dominance);
 - estimating the resistance-allele frequency in the original population;
 - determining whether the resistance-allele Frequency is increasing by analyzing field collections in subsequent years sampled from the same site where the resistance allele(s) was originally collected;
 - determining the geographic distribution of the resistance allele by analyzing field collections in subsequent years from sites surrounding the site where the resistance allele(s) was originally collected.

Should field-relevant resistance be confirmed, and the resistance appears to be increasing or spreading, the registrant will consult with the Agency to develop and implement a case-specific resistance management action plan.

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(2) Investigation of Reports of Unexpected Levels of Damage by the Target Pests:

The registrant will follow up on grower, extension specialist or consultant reports of unexpected levels of damage by the lepidopteran pests listed on the pesticide label. The registrant will instruct its customers to contact them if such incidents occur. The registrant will investigate all legitimate reports submitted to the company or the company's representatives.

If reports of unexpected levels of damage lead to the suspicion of resistance in any of the key target pests (ECB, SWCB, and CEW), the registrant will implement the actions described below, based on the following definitions of *suspected resistance* and *confirmed resistance*.

Suspected resistance

EPA defines *suspected resistance* to mean field reports of unexpected levels of insect feeding damage for which:

- the corn in question has been confirmed to be lepidopteran-active Bt corn;
- the seed used had the proper percentage of corn expressing Bt protein;
- the relevant plant tissues are expressing the expected level of Bt protein; and
- it has been ruled out that species not susceptible to the protein could be responsible for the damage, that no climatic or cultural reasons could be responsible for the damage, and that there could be no other reasonable causes for the damage.

The Agency does not interpret *suspected resistance* to mean grower reports of possible control failures or suspicious results from annual insect monitoring assays, nor does the Agency intend that extensive field studies and testing be undertaken to confirm scientifically the presence of insects resistant to Bt corn in commercial production fields before responsive measures are undertaken.

If resistance is *suspected*, the registrant will instruct growers to do the following:

- Use alternative control measures in the Bt corn fields in the affected region to control the target pest during the immediate growing season.
- Destroy Bt corn crop residues in the affected region within one month after

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harvest with a technique appropriate for local production practices to minimize the possibility of resistant insects over-wintering and contributing to the next season's target pest population.

Additionally, if possible, and prior to the application of alternative control measures or destruction of crop residue, the registrant will collect samples of the insect population in the affected fields for laboratory rearing and testing. Such rearing and testing shall be conducted as expeditiously as practical.

Confirmed resistance

EPA defines *confirmed resistance* to mean, in the case of field reports of unexpected levels of damage from the key target pests, that all the following criteria are met:

- There is >30% insect survival and commensurate insect feeding in a bioassay, initiated with neonate larvae, that uses methods that are representative of exposure to Bt corn hybrids under field conditions (ECB and SWCB only).
- In standardized laboratory bioassays using diagnostic concentrations of the Bt protein suited to the target pest in question, the pest exhibits resistance that has a genetic basis and the level of survivorship indicates that there may be a resistance allele frequency of ≥ 0.1 in the sampled population.
- In standardized laboratory bioassays, the LC_{50} exceeds the upper limit of the 95% confidence interval of the LC_{50} for susceptible populations surveyed both in the original baselines developed for this pest species and in previous years of field monitoring.

(3) Response to Confirmed Resistance in a Key Target Pest as the Cause of Unexpected Levels of Damage in the Field

When field resistance is *confirmed* (as defined above), the following steps will be taken by the registrant:

- EPA will receive notification within 30 days of resistance confirmation;
- Affected customers and extension agents will be notified about confirmed resistance within 30 days;
- Monitoring will be increased in the affected area and local target pest populations will be sampled annually to determine the extent and impact of resistance;
- If appropriate (depending on the resistant pest species, the extent of resistance, the timing of resistance, and the nature of resistance, and the availability of suitable alternative

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control measures), alternative control measures will be employed to reduce or control target pest populations in the affected area. Alternative control measures may include advising customers and extension agents in the affected area to incorporate crop residues into the soil following harvest to minimize the possibility of over-wintering insects, and/or applications of chemical insecticides;

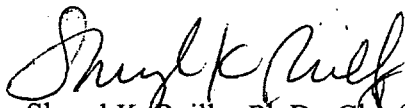
- Unless otherwise agreed with EPA, stop sale and distribution of the relevant lepidopteran-active Bt corn hybrids in the affected area immediately until an effective local mitigation plan approved by EPA has been implemented;
- The registrant will develop a case-specific resistance management action plan within 90 days according to the characteristics of the resistance event and local agronomic needs. The registrant will consult with appropriate stakeholders in the development of the action plan, and the details of such a plan shall be approved by EPA prior to implementation;
- Notify affected parties (e.g. growers, consultants, extension agents, seed distributors, university cooperators and state/federal authorities as appropriate) in the region of the resistance situation and approved action plan; and
- In subsequent growing seasons, maintain sales suspension and alternative resistance management strategies in the affected region(s) for the Bt corn hybrids that are affected by the resistant population until an EPA-approved local resistance management plan is in place to mitigate the resistance.

A report on results of resistance monitoring and investigations of damage reports must be submitted to the Agency annually by August 31st each year for the duration of the conditional registration.

If these conditions are not complied with, the registration will be subject to cancellation in accordance with FIFRA section 6(e). Your release for shipment of Cry1F corn constitutes acceptance of these conditions.

A stamped copy of the FIFRA label is enclosed for your records.

Sincerely,


 Sheryl K. Reilly, Ph.D., Chief
 Microbial Pesticides Branch
 Biopesticides and Pollution
 Prevention Division (7511P)

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Herculex™ XTRA Insect Protection

Active Ingredient:

Bacillus thuringiensis Cry1F protein and the genetic material necessary for its production (plasmid insert PHI8999; event TC1507) in corn0.000288 – 0.001740%**

Bacillus thuringiensis Cry34Ab1 insecticidal crystal protein and the genetic material necessary for its production (plasmid insert PHP17662; event DAS-59122-7) in corn.....0.006480 – 0.016840%

Bacillus thuringiensis Cry35Ab1 insecticidal crystal protein and the genetic material necessary for its production (plasmid insert PHP17662; event DAS-59122-7) in corn.....0.001950 – 0.006760%

Inert Ingredient:

Substance produced by a marker gene and its controlling sequences in corn0.000003 – 0.001510%

**% total protein on a dry wt. basis as expressed in corn plant cells (whole plant)

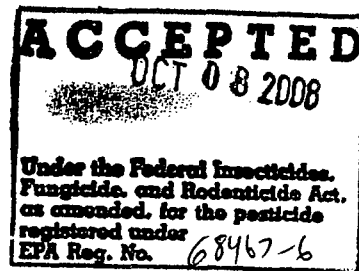
**KEEP OUT OF REACH OF CHILDREN
CAUTION**

EPA Reg. No. 68467-6

EPA Est. 029964-IA-001

Mycogen Seeds
c/o Dow AgroSciences LLC
9330 Zionsville Road
Indianapolis, IN 46268

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DIRECTIONS FOR USE

It is a violation of federal law to use this product in any manner inconsistent with its labeling.

The subject registration automatically expires at midnight on midnight September 30, 2010.

The plant-incorporated protectant product must be used as specified in the terms and conditions of the registration.

Herculex XTRA combines the insect protection features of Herculex I and Herculex RW in the same corn hybrid (inbred). Herculex XTRA hybrids protect corn crops from leaf, stalk and ear damage caused by Lepidopteran corn pests such as the European corn borer, and root damage caused by corn rootworm larvae. In order to minimize the risk of the corn pests developing resistance to Herculex XTRA corn, an insect resistance management plan must be implemented.

Grower agreements will specify that growers must adhere to the refuge requirements that will be described in the Product Use Guide for Herculex XTRA corn or other applicable product use documents.

Growers are instructed to read information on insect resistance management. The following information regarding refuge placement for commercial production must be included in the Growing Guide.

The use of Cry1F x Cry34/35Ab1 corn requires accompanying refuge corn for both the Cry1F and Cry34/35Ab1 components that meets the requirements of the individual traits, described below. The refuge for both traits may be combined by planting non-*Bt* corn as the refuge (see C below), or the refuge for each trait may be planted separately (see A. and B. below)

For the separate refuges, corn rootworm-resistant *Bt* corn (e.g., Herculex RW) may be planted in the lepidopteran refuge for the Cry1F component and lepidopteran-resistant *Bt* corn (e.g., Herculex I) may be planted in the corn rootworm refuge for the Cry34/35Ab1 component. Depending on cropping practices, pest problems, and pest management options employed on any given farm, growers may need to choose different refuge arrangements for different fields. Possible options include: two refuge blocks (one for rootworm, one for Lepidoptera) can be planted within one field, or strips can be used for either refuge. Alternatively, a block of Herculex RW corn can serve as an in-field lepidopteran refuge for one field planted to Cry1F X Cry34/35Ab1 and an external lepidopteran refuge for separate fields planted to Cry 1F X Cry34/35Ab1, while the rootworm refuge is planted as Herculex I corn in an external adjacent field. In all options, size and management of each individual refuge must be followed as described in A. and B. below.

Other refuge designs and combinations are permissible as long as in all cases the size and management of each refuge are described in A., B., and C., below.

A. Lepidopteran refuge for the Cry1F component.

1. *Refuge size, Corn-Growing Areas* (= corn belt and other non corn/cotton-growing regions). The use of Cry1F x Cry34/35Ab1 corn requires an accompanying 20% refuge consisting of non-*Bt* corn or non-lepidopteran resistant *Bt* corn.
2. *Refuge size, (Corn/Cotton-growing areas)*. * The use Cry1F x Cry34/35Ab1 corn requires an accompanying 50% refuge consisting of non-*Bt* corn or non-lepidopteran resistant *Bt* corn.
3. *Refuge location*.
 - The lepidopteran refuge can be planted in a separate field not more than ½ mile of the Cry1F x Cry34/35Ab1 field.
 - The lepidopteran refuge can be planted within the Cry1F x Cry34/35Ab1 field as blocks (e.g. along the edges or headlands)

- The lepidopteran refuge can be planted within the Cry1F x Cry34/35Ab1 field as strips across the field at least four rows wide.

4. *Refuge management.*

- Insecticide treatments for control of European corn borer, corn earworm, southwestern corn borer and other lepidopteran target pests listed on the label, grower guides, or other educational material may be applied only if economic thresholds are reached for one or more of these target pests. Economic thresholds will be determined using methods recommended by local or regional professionals (e.g. Extension Service Agents, crop consultants). Microbial *Bt* insecticides must not be applied to non-*Bt* corn and/or non-lepidopteran resistant *Bt* corn refuges.

* Cotton growing areas consist of the following states Alabama, Arkansas, Georgia, Florida, Louisiana, North Carolina, Mississippi, South Carolina, Oklahoma (only the counties of Beckham, Caddo, Comanche, Custer, Greer, Harmon, Jackson, Kay, Kiowa, Tillman, Washita), Tennessee (only the counties of Carroll, Chester, Crockett, Dyer, Fayette, Franklin, Gibson, Hardeman, Hardin, Haywood, Lake, Lauderdale, Lincoln, Madison, Obion, Rutherford, Shelby, and Tipton), Texas (except the counties of Carson, Dallam, Hansford, Hartley, Hutchinson, Lipscomb, Moore, Ochiltree, Roberts, and Sherman), Virginia (only the counties of Dinwiddie, Franklin City, Greensville, Isle of Wight, Northampton, Southampton, Suffolk City, Surrey, Sussex) and Missouri (only the counties of Dunkin, New Madrid, Pemiscot, Scott, Stoddard).

B. Corn rootworm refuge for the Cry34/35Ab1 component.

1. *Refuge size.* The use of Cry1F x Cry34/35Ab1 corn requires an accompanying 20% refuge consisting of non-*Bt* corn or non-corn rootworm-resistant *Bt* corn.
2. *Refuge location.* The rootworm refuge is required to be planted within or adjacent (e.g. across the road) to the Cry1F x Cry34/35Ab1 corn field.
3. *Refuge management options.* The rootworm refuge can be managed in such a way that there is little or no yield loss to rootworms, but must be managed in a way that it is sufficiently productive of susceptible rootworm adults.
 - The in-field rootworm refuge options may be planted as a single block or as a series of strips measuring at least four (4) crop rows wide.
 - Seed mixtures of Cry1F x Cry34/35Ab1 and rootworm refuge corn are not permitted.
 - If the rootworm refuge is planted on rotated ground, then Cry1F x Cry34/35Ab1 corn must also be planted on rotated ground.
 - If the rootworm refuge is planted in continuous corn, the Cry1F x Cry34/35Ab1 field may be planted on either continuous or rotated land (option encouraged where WCRW rotation-resistant biotype may be present).
 - Application of soil insecticide is permitted in the rootworm refuge.
 - Seed treatment is permitted in the rootworm refuge, either at a rate for rootworm protection or at a rate for controlling secondary soil pests.
 - If aerial insecticides are applied to the rootworm refuge for control of CRW adults, the same treatment must also be applied in the same time-frame to Cry1F x Cry34/35Ab1 corn.
 - Pests other than adult corn rootworms can be treated on the rootworm refuge acres without treating the Cry1F x Cry34/35Ab1 acres only if treatment occurs when adult corn rootworms are not present or if a pesticide without activity against adult corn rootworms is used. Pests on the Cry1F x Cry34/35Ab1 acres can be treated as needed without having to treat the rootworm refuge.
 - The rootworm refuge can be planted to any corn hybrid that does not express PIPs for rootworm control (e.g. lepidopteran-protected *Bt* corn, herbicide-tolerant corn, or conventional corn).

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- The rootworm refuge and Cry1F x Cry34/35Ab1 corn should be sown on the same day, or with the shortest window possible between planting dates, to ensure that corn root development is similar among varieties.
- Growers are encouraged to plant the rootworm refuge in the same location each year, as it allows the rootworm population to remain high and the durability of the trait is extended. This option may be preferable to growers who wish to only think of their refuge design once and for growers who grow continuous corn. However, for those growers who need to employ crop rotation, a fixed refuge would be impractical.

C. For the combined refuge option (i.e. the lepidopteran refuge combined with the rootworm refuge by planting non-Bt corn), the refuge must be planted and managed such that it is consistent with the requirements of the two individual traits, as follows

1. *Refuge size* shall be 20% in corn-growing areas and 50% in cotton-growing areas (see list labeled with " * " under A).
2. *Refuge location.* The combined refuge is required to be planted within or adjacent (e.g. across the road) to the Cry1F x Cry34/35Ab1 corn field.
3. *Refuge management options*
 - The in-field refuge options must be planted as a single block or as a series of strips measuring at least four (4) rows wide.
 - Seed mixtures of Cry1F x Cry34/35Ab1 and refuge corn are not permitted.
 - If the combined refuge is planted on rotated ground, then the Cry1F x Cry34/35Ab1 corn must also be planted on rotated ground.
 - If the combined refuge is planted on continuous corn, the Cry1F x Cry34/35Ab1 field may be planted on either continuous or rotated land (option encouraged where WCRW rotation-resistant biotype may be present).
 - Application of soil insecticide for corn rootworm control is permitted in the combined refuge.
 - Seed treatment is permitted in the combined refuge, either at a rate for rootworm protection or at a rate for controlling secondary soil pests.
 - If aerial insecticides are applied to the combined refuge for control of CRW adults, the same treatment must also be applied in the same timeframe to Cry1F x Cry34/35Ab1 corn.
 - Insecticide treatments in the combined refuge for control of European corn borer, corn earworm, southwestern corn borer, fall armyworm, black cutworm, western bean cutworm, sugarcane borer, lesser corn stalk borer, or southern corn stalk borer may be applied only if economic thresholds are reached for one or more of these target pests. Economic thresholds will be determined using methods recommended by local or regional professionals (e.g. Extension Service Agents, crop consultants). These pests can be treated with CRW-labeled insecticide on the combined refuge acres without treating the Cry1F x Cry34/35Ab1 acres only if treatment occurs when adults corn rootworms are not present. Microbial *Bt* insecticides must not be applied to the common refuges.
 - Pests other than adult corn rootworms can be treated with CRW-labeled insecticide on the combined refuge acres without treating the Cry1F x Cry34/35Ab1 acres only if treatment occurs when adults corn rootworms are not present. Pests on the Cry1F x Cry34/35Ab1 acres can be treated as needed without having to treat the refuge.
 - The combined refuge can be planted to any corn hybrid that does not express PIPs for lepidopteran or rootworm control (i.e. herbicide tolerant corn or conventional corn).
 - The combined refuge and Cry1F x Cry34/35Ab1 corn should be sown on the same day, or with the shortest window possible between planting dates, to ensure that corn root development is similar among varieties.

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Use Pattern

Crop	Pests
Field corn	black cutworm corn earworm European corn borer fall armyworm Mexican corn rootworm northern corn rootworm southwestern corn borer western bean cutworm western corn rootworm lesser corn stalk borer southern corn stalk borer sugarcane borer

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