8-16-93

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 16 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: SAB Review of Supplemental Information Submitted to Support the Registration of CYD-X, a Virus-Based Insecticidal Product (DP Barcode D193272; Submission No. S440142; I.D. No. 058971-U CYD-X; MRID Nos.: 427218-01 through -03; Shaughnessy No. 122201)

TO: Linda Hollis/Phil Hutton (PM-18)
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Registration Division (H7505C)

FROM: J. Thomas McClintock, Ph.D., Microbiologist
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THROUGH: Roy D. Sjoblad, Ph.D., Section Head
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ACTION REQUESTED: Crop Genetics International, Inc. (CGI) previously submitted a registration application for CYD-X, a virus-based insecticidal product containing capsules of Cydia pomonella (the codling moth) granulosis virus (CpGV). During the initial review of the registration package, SAB noted several deficiencies in the Product Identity/Chemistry and Mammalian Toxicology studies (see June 1, 1993 memorandum from J. T. McClintock to L. Hollis/P. Hutton). In response to these deficiencies, CGI submitted supplemental data and/or information to support the registration of CYD-X. Summarized below is CGI's response to the deficiencies noted by SAB.

CONCLUSION: With the exception of submitting a revised CSF (151A-10) and fulfilling the requirements for 152A-16 (Cell Culture Assay), all Product Identity/Chemistry and Mammalian Toxicology studies have been satisfied.

DISCUSSION: To fulfill the Product Identity/Chemistry requirements the following information was requested and is listed by Guideline numbers with the accompanying response by CGI.

151A-10. (b). Confidential Statement of Formula (CSF). SAB requested a revised CSF stating that the product CYD-X contain capsules of the granulosis virus of *Cydia pomonella* (codling moth)

as the active ingredient (a.i.). Additional modifications were noted and specified by SAB.

CGI's Response: No response. These deficiencies are still outstanding.

Although not requested additional restriction profiles and analyses were submitted to further characterize the CpGV isolate (lot No. 052991) intended for registration (see attached). Using EcoRI, BamHI, SalI, and XhoI, the CpGV isolate was determined to be nearly identical to the Mexican CpGV isolate. The molecular weights for each restriction fragments were determined; the estimated molecular weight of the total viral genome was determined to be approximately 121.9 kb.

151A-11. Manufacturing Process. Since the a.i. is produced *in vivo*, SAB requested information on the procedures used to insure a healthy or disease-free insect colony.

CGI's Response: Sufficient information on insect colony maintenance was submitted outlining the various procedures used to ensure a healthy colony. [redacted]

151A-12. Discussion of Formation of Unintentional Ingredients. Since CYD-X is produced in a biological system (i.e. *in vivo*), SAB requested information on the methodologies used to detect the presence of mammalian pathogens in each "production" batch. In light of the fact that an incomplete QC/QA procedure was described an intraperitoneal (IP) or acute oral screen for each independent batch was recommended.

CGI's Response: [redacted]

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

the course of the study the production batch is considered "unsatisfactory" and presumably discarded.

SAB Comments: Given that CGI has now completely described a standard procedure to detect potential human coliforms in each production batch the necessity of an IP injection screen becomes less important when considering the likelihood of human pathogens appearing independent of a positive MPN screen.

151A-13. Analysis of Samples. In the original submission the registrant stated that "...the fundamental difference of this product from a traditional chemical renders this requirement inappropriate." This rational was inappropriate. SAB requested that CGI provide a discussion on the methods used to analyze each sample or production batch for the quantity of occlusion bodies.

CGI's Response: An adequate discussion on the composition of the product including impurities was presented. CGI emphasized that since this product is produced in codling moth larvae the level of inert ingredients will vary from batch to batch and that quality control measures are in place to "...insure that no toxic contaminants will occur in the inert ingredients of this product." (see 151A-12). The discussion of the methods used to analyze each batch is presented below.

151A-15. Certification of Ingredient Limits. Since the certified limits must be supported by an acceptable analytical method, SAB requested that the procedure used for enumeration and/or quantification of the number of occlusion bodies per batch be specified.

CGI's Response: A protocol for sampling and enumerating CpGV occlusion bodies and information on the procedure was submitted. [redacted]

152A-16. Cell Culture. A waiver request for this study was previously denied by SAB based on the existing data from the open literature. SAB recommended that the applicant demonstrate the ability or inability of CpGV to replicate in mammalian cell lines.

CGI's Response: CGI has requested a waiver for this study. No additional information was submitted which would further support the waiver request.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

NOTE: In a recent correspondence with SAB, CGI stated that the results from the cell culture study were completed. However, the viral inoculum was of a titer apparently insufficient to produce a desired effect. Consequently, CGI decided to repeat this study. This requirement still remains outstanding. SAB also stated that CGI needed only to challenge mammalian cell lines with CpGV alkaline-liberated virions and monitor the cells for any adverse effects by light microscopy.

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Page _____ is not included in this copy.

Pages ~~14~~ (5) through ~~16~~ (7) are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.