NATIONAL BIOSAFETY BOARD DECISION

APPLICATION FOR APPROVAL TO RELEASE PRODUCTS OF TMOF_YEAST (GENETICALLY-MODIFIED *Pichia pastoris*) THAT FORMULATED INTO MOUSTICIDE RICE HUSK (RH) AND MOUSTICIDE WETTABLE POWDER (WP)

NBB REF. NO: JBK(S) 602-1/1/5
APPLICANT: ENTOGENEX INDUSTRIES SDN BHD
DATE OF DECISION: 26 JULY 2011

The National Biosafety Board (NBB) on the 26 July 2011 granted approval with terms and conditions to an application from EntoGeneX Industries Sdn. Bhd. (EntoGeneX) for release activities of TMOF_Yeast.

This approval permits the release of the "heat-killed" TMOF_Yeast containing TMOF (Trypsin Modulating Oostatic Factor) peptide which is formulated into Mousticide RH and Mousticide WP. The products are aimed at controlling the *Aedes* mosquito larvae population.

The recommendation of the Genetic Modification Advisory Committee (GMAC) to the NBB was for an approval with terms and conditions in accordance with the provisions of subsections 16(3) and 16(4) of the Biosafety Act for the use of Mousticide WP and Mousticide RH (produced from CEPP, UTM). This recommendation was based upon the condition that the issues identified in the environmental risk assessment be thoroughly reassessed for the accumulative impact from long-term usage of this product, or if TMOF is used for the formulation of another type of end product, as there may be variables in the effectiveness of the protocols used as well as variations in the risk exposure pathways. Proper risk management strategies are to be followed as stipulated through the terms and conditions imposed (Appendix 1). These conditions include restrictions in distribution sites, such as finished, treated drinking water sources and also the imposition in mandatory labeling; for which product handling and safety instructions are to be clearly displayed. In addition to supporting data provided from studies done on the product, further studies shall carried out, focusing on local organisms, in a prescribed period and the results reported back to NBB.

If the Chemical Engineering Pilot Plant (CEPP), Universiti Teknologi Malaysia (UTM), is to be used for the production of TMOF_Yeast, specific conditions shall be fulfilled before any production activity takes place. The suitability of the facility for the production shall be based on compliance to the GMAC recommendations.

Public consultation for this application was done from 23 June 2011 until 8 July 2011. Concerns raised by the public were addressed and taken into consideration when NBB made the decision.

The basis for this decision also includes the following:

- That impact studies of the product had already been conducted by the Malaysian Palm Oil Board (MPOB) on the oil palm pollinating weevil, and the product was endorsed as safe by the Chairman of MPOB;
- That data had been provided in the Environmental Protection Agency (USA) report on the safety of the product. However, further studies have been imposed on the applicant; and
- That the product is intended for use to control outbreaks of dengue fever, which is one of the critical health issues in Malaysia.

Appendix 1

SUMMARY OF TERMS AND CONDITIONS FOR THE CERTIFICATE OF APPROVAL

Release activities of MOUSTICIDE™ Wettable Powder (WP) and MOUSTICIDE™ Rice Husk (RH)

PART A

INFORMATION AND/OR DOCUMENTATION THAT SHALL BE SUBMITTED TO THE NATIONAL BIOSAFETY BOARD (NBB) BEFORE RELEASE

1) The applicant is required to provide information on the manufacturing plant's Biosafety Level (BSL) and data on the heat kill process. The quality control procedure shall be properly validated or modified to ensure that the heat kill process is sufficiently effective for a 6-log reduction in the number of viable cells.

2) If the Chemical Engineering Pilot Plant (CEPP) in Universiti Teknologi Malaysia, Johor, is the facility to be used for production of TMOF_Yeast, the specific conditions imposed by the Genetic Modification Advisory Committee (GMAC) as listed in Part C shall be adhered to and complied with to ensure containment and proper management.

3) Proof of compliance to these conditions must be provided through a visit to the facility by GMAC members.

4) If the production is to be done in a facility other than CEPP, a Notification of that chosen facility for contained use activity must be submitted to the National Biosafety Board.

PART B

CONDITIONS FOR THE RELEASE

1) Release is limited to TMOF _Yeast (Technical Grade Active Ingredient, TGAI) in the formulations of MOUSTICIDE™ Wettable Powder (WP) and MOUSTICIDE™ Rice Husk (RH) as end products. For any other formulation, or if TMOF_Yeast is produced again in another facility, reassessment by NBB and GMAC are required.

2) Both MOUSTICIDE™ products shall not be applied to water bodies and waterways such as finished, treated drinking water sources.

3) The requirement for proper labeling is imposed; product handling and safety instructions shall be provided together with the products. These instructions shall include the need for personal protective equipment (PPE) and proper usage procedures covering notification and follow-up medical monitoring of staff handling the product.

4) Post-release environmental monitoring shall be undertaken by the applicant to negate long-term cumulative effects on the oil palm weevil, other non-target organisms (in particular

aquatic organisms) and human health from repeated applications of MOUSTICIDE™WP and MOUSTICIDE™ RH.

5) The applicant shall conduct thorough studies[i] in the following areas and to **report the progress and results of these studies to NBB on a quarterly basis from the date of approval**. The final results of these studies shall be communicated to the Board within 24 months of the date of approval:

i) Possible toxic effects on the oil palm pollinating weevil. More comprehensive and properly designed studies are needed, using laboratory-reared weevils of the same age, to (a) examine egg development and oviposition by treated adult females (*vis-a-vis* an untreated check) because there is a possible implication on egg development; and (b) examine the conditions of the midgut peritropic membrane of the weevils which survive but may have been impaired in terms of subsequent development;

ii) Effect of MOUSTICIDE™WP and MOUSTICIDE™ RH on local fauna. These studies are to establish the toxicology of Mousticide on (a) Focal local insect species that were not covered in the EPA report which are significant to other plants/crops (e.g. cocoa, rubber, pepper, rice, etc.); and (b) Focal species of aquatic organisms because applications are targeted on aquatic environments;

iii) Synergistic effect of TMOF with other biopesticides. These studies are to determine the possibility that combining TMOF with Bti or other biopesticides may lead to an increased spectrum of non-target organisms, or an increased toxicity level in mildly-affected organisms; and

iv) Impact of TMOF/ MOUSTICIDE™WP and MOUSTICIDE™ RH on human health. These studies are to examine the impact of TMOF/_MOUSTICIDE™WP and MOUSTICIDE™ RH on human health from repeated exposure to the insect proteins *via* inhalation or skin contact during the spraying of the wettable powder in an aquatic environment which is likely to happen if PPE is not used.

PART C

ACTIONS FOR IMPROVEMENT OF MANAGEMENT FOR THE CONTAINED USE FACILITY AT THE CHEMICAL ENGINEERING PILOT PLANT (CEPP), UNIVERSITI TEKNOLOGI MALAYSIA (UTM)

Following up on the visit by representatives of GMAC to the three facilities (Cell Propagation Room, Bioprocessing Facility and Spray Drying Facility at CEPP, UTM) on 6 October 2009, a few specific conditions were imposed on the applicant as conditions that are to be complied with. These conditions include an improvement to facility design, administrative controls and engineering controls. Compliance to the imposed conditions shall be evaluated by GMAC.

[i] The United States Environmental Protection Agency (EPA) assessment of Trypsin Modulating Oostatic Factor (TMOF) was done for manufacturing use only, and any **end use product using TMOF shall be evaluated individually** to determine risk and labeling issues. This report specifies that for the evaluation of a new end use product using TMOF, additional information must be provided such as data on food clearance/tolerance, toxicity of the end product on non-target organisms, efficacy of the product, and impact on endangered invertebrate species.