Health Canada
Santé Canada

Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

2008-2513

DEC 16 2009

Warren Smith
Valent BioSciences Corporation
870 Technology Way
Libertyville, IL
USA 60048

Dear Mr Smith:

Re: Notice of Objection – RVD2008-18 *Bacillus thuringiensis*

We have carefully reviewed your Notice of Objection, filed in July of 2008, regarding the Health Canada Pest Management Regulatory Agency (PMRA) decision to continue the registration of *Bacillus thuringiensis* (RVD2008-18). We are aware of your long-standing interest in *Bacillus thuringiensis*, and continue to make every effort to answer your questions and address your concerns.

Under the *Pest Control Products Act*, any person who believes there is a scientific basis for reconsideration of a decision to which subsection 28(1) applies can file a Notice of Objection within 60 days of the publication of the decision. Objections are expected to focus on the scientific basis of the decision related to health and environmental risks, the value of the pesticide and the need for this decision to be taken to an external panel of experts for consideration of the scientific argument presented in the Notice and to obtain advice to the Minister in that regard.

When a notice of objection is filed, a team of PMRA scientists, who were not involved in the original decision, is established. The team considers the scientific basis for the objection and determines if the criteria for the establishment of a review panel have been met.

Criteria for establishing a review panel include:

a. whether the information in the notice raises scientifically founded doubt as to the validity of the evaluation or re-evaluation of the health and environmental risks and the value of the pesticide; and
b. whether the advice of a panel of expert scientists would assist in addressing the objection.

.../2

Many of the concerns you raised in your objection were addressed during the extensive review and consultation process for the re-evaluation of *Bacillus thuringiensis*, and in our previous communications with you previously. Our team of PMRA scientists has carefully and extensively reviewed your questions and concerns, and has responded to each item separately in the attached document with information that was considered in the re-evaluation decision of *Bacillus thuringiensis*. The team did not identify any scientifically founded doubt with respect to the validity of the PMRA re-evaluation decision in the information you provided in your objection. As a result this notice of objection does not fulfill the criteria to establish a review panel to reconsider the decision for continued registration of *Bacillus thuringiensis*. However, some statements will be amended on the product labels, as outlined in the attached detailed response.

We trust that the information provided in the attached detailed response provides some clarity to the issues you raised. The PMRA continues to put human health and the environment at the forefront of our regulatory activities, and will only register products for which there is reasonable certainty that no harm will result from their use as directed, including *Bacillus thuringiensis*.

Sincerely,

Marion Law
Chief Registrar
PEST MANAGEMENT REGULATORY AGENCY

Attachment:
Detailed Response to Notice of Objection

Attachment: A
Sub. No. 2008-2513

Detailed Response to Notice of Objection – RVD2008-18 *Bacillus thuringiensis*

The notice of objection, filed under subsection 35(1) of the *Pest Control Products Act* (PCPA), by Mr. Warren Smith regarding the re-evaluation decision for *Bacillus thuringiensis* has now been reviewed and assessed in accordance with the Act and Regulations.

The following information was received and reviewed in support of the notice of objection:

- Valent BioSciences Corporation (VCB) Notice of Objection to PMRA Decision on Label Requirements for Bacillus thuringiensis (rationale)
- Response to Potential Sensitizer precautionary statement for *Bacillus thuringiensis* subsp. *Kurstaki* strain ABTS-351.

Issues raised in the Notice of Objection are **bolded**, PMRA responses are not.

1) Aquatic Statement

Valent BioSciences Corp is concerned about the need of label language specific to Btk under DIRECTIONS FOR USE - 'Do not apply directly to aquatic habitats'.

This language as written will preclude the primary intended uses for some of the Btk products. Standard label language can prevent a product from being used for an approved use because it makes practical application of the product impossible. Bts do not pose actual aquatic concerns (please see some of the scientific indications of this below). Hence additional label language needs to be developed which clearly indicates that forestry uses of Bt, do not present a direct application to aquatic habitats.

Labels already clearly indicate the applications permitted. There are no aquatic uses on the labels for Btk. The concern comes on possible precautionary statement interpretation/liability when doing aerial Btk applications on, for example, large forestry tracks that may contain streams, prairie potholes, creeks, etc. While the application is not 'directed' at aquatic habitats overspray cannot be strictly controlled as aquatic habitats intermingled in forests are overflown.

Btk sprays have been undertaken for years in Canada. Projects undertaken by Environment Canada continue to show the innocuousness of Bt to the environment. For example the study: PROJECT, Ecotoxicology of Biotechnology Products: The case of *Bacillus thuringiensis* (www.qc.ec.gc.ca/csl/pro/pro032fg-e html)

Gives the following conclusion:

'Main Results to Date

Results have shown that although Bt crystals appear rather stable, the toxin is found in very low concentrations in the aquatic environment and degrades more quickly in water than in soil. Work is continuing in order to determine the presence and persistence of the gene and of the Bt corn toxin (CrylAb) in the aquatic environment'

During nearly 45 years of registration and about 30 years of wide scale aerial and terrestrial application around the world, Btk applications have not resulted in any significant aquatic effects when applied in accordance with the label. The proposed wording is not supported by fact. The science clearly shows the little risk Bts poses to aquatic habitats in all their complexity.

The paper: Functional Effects of the Bacterial Insecticide *Bacillus thuringiensis* var. *kurstaki* on Aquatic Microbial Communities. David P. Kreutzweiser[a], J. Lawrence Gringorten[a], David R. Thomas[a] and Jason T. Butcher

[a] Canadian Forest Service, 1219 Queen St. East, Sault Ste. Marie, Ontario, Canada, P6A 5M7
Ecotoxicology and Environmental Safety Volume 33, Issue 3, April 1996, Pages 271-280

Indicates: 'These results from laboratory and controlled field experiments indicate that contamination of watercourses with Btk is unlikely to result in significant adverse effects on microbial community function in terms of detrital decomposition.'
In addition, an up-to-date book by two New Zealand scientists covers the potential environmental impacts of Bt in great detail.

Glare, T.R. and O'Callaghan, M. 2000. *Bacillus thuringiensis*; Biology, Ecology and Safety. John Wiley and Sons, Chichester, UK. 350 pp.

The World Health Organization have also recently reviewed the environmental impacts of Bt (Anonymous 1999. Microbial Pest Control Agent *Bacillus thuringiensis,* Environmental Health Criteria 217. World Health Organization, Geneva).

Both publications offer no significant effects on aquatic systems by Bts. Water quality should not be directly affected by Btk as it is not likely to affect most aquatic organisms. Some North American laboratory studies have shown decreases in detritus decomposition rates at high doses of Btk. However, these effects are unlikely in the environment because of the lower doses of Btk used and the purification processes in natural systems (USDA 1995)

VBC Proposal: As indicated in the Bt Re-evaluation Document, there are no aquatic impacts associated with the use of Bt. This proposed label language should be modified/present an addendum to prevent the liability questions raised by the language in its current state. The control of pests that are present in vegetation over waters should not be considered a direct application of pesticide to water. Standard label language which is appropriate and feasible for agricultural uses, is not workable for forestry applications. Labels should be reflective of actual concerns and safety precautions that are in fact called for."

The statement, "Do not apply directly to aquatic habitats ...", was intended to prevent all aquatic uses (direct applications) of Btk-based products since there are no registered aquatic uses for this microbial pest control agent. The intent was not to limit indirect aquatic applications which may occur during forestry applications, especially in small aquatic habitats that are intermingled in

forests. As noted in the Re-evaluation Decision Document, RVD2008-18, *Bacillus thuringiensis*, PMRA recognized that the statement could have alternate meanings to other jurisdictions so the following alternate statement was drafted in consultation with stakeholders:

"As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests."

The previous statement will no longer be required on the label. In addition, the PMRA will no longer require the following statement under the "Directions for use" section since it makes reference to sensitive aquatic habitats:

"BEFORE AERIAL APPLICATIONS TO FORESTS - Consult the most recent provincially approved topographic maps of the area to be treated (1: 50,000) or more up-to-date information (e.g. GPS systems) to identify sensitive aquatic habitats. Sensitive aquatic habitats include:

a) All running (lotic) and standing (lentic) water bodies, including impoundments, beaver ponds and bog ponds, that appear on the map or GPS system;
b) Running (lotic) and standing (lentic) water bodies that do not appear on the map or GPS system but are visible from the air."

2) Precautionary Statement

"Valent BioSciences Corp. believes precautionary wording should be specific to the product being labeled. Thus we agree with the indication that "CAUTION EYE IRRITANT" may be waived if data is submitted that indicates that eye irritation would not be an issue with a particular Bt product.

Additionally, the Re-evaluation Decision Document would require that Bt labels must contain precautionary statements indicating that the product is a POTENTIAL SENSITIZER. VBC believes that data should also be considered for determining language on sensitization. While bacterial products, due to their protein content may have the potential to be sensitizers, if data is sufficient to indicate that sensitization would not be an issue for a specific strain and/or formulation, then the requirement for a sensitization statement should also have the possibility to be waived.

In its PACR for Bts, PMRA has evaluated a large number of publications and numerous surveillance reports of large scale human exposure. None of the epidemiological studies identified sensitization from, at least, specific Btk formulations. The potential for sensitization should be able to be waived when there is a large volume of work which would indicate that a specific product does not in fact cause sensitization.

A science based risk evaluation should take into consideration all studies available, for example, where sensitization studies with standard protocols indicate a lack of sensitization there should be no requirement for cautionary statements indicating the product is a potential sensitizer.
Additional scientific evidence as to the different potential of different microbial species to elicit sensitization is attached as Appendix I.

VBC Proposal:

Label language should be left open to being modified by specific data."

The current PMRA policy on the sensitization potential of various microbial pest control agents was adopted because of the complex nature of microbial pest control products, and the lack of appropriate standardized test methods. Microbial pest control products contain numerous biological macromolecules associated with not only the microbial pest control agent, but those associated with possible microbial contaminants, and growth medium constituents as well. Many of these biological materials could, in theory, induce allergies in susceptible individuals via a number of possible routes of exposure. PMRA is aware of standard OECD and U.S. EPA test methods for evaluating the sensitization potential of products, however, these methods only measure the sensitization potential of compounds on a small number of test animals via the dermal/intradermal route. Since these studies do not include a larger number of animals to account for natural variation in any given population and only measure the sensitization potential of samples via the dermal/intradermal route (e.g., not inhalation or intranasal routes), they do not entirely address PMRA's concerns with these types of product. Faced with these challenges, the PMRA chose to waive sensitization testing for all microbial-based products and require mitigative label statements to minimize exposure rather than request elaborate and onerous studies.

To address the objector's original concern, the PMRA has reviewed some data and would consider new data to re-evaluate the requirement for product labeling, however, for the reasons noted above, appropriate data are difficult to generate for microbial pest control agents, especially new ones with little or no history of use without widespread reporting of adverse effects. That said, *B. thuringiensis*-based products have a long history of use in many countries, including Canada and the United States. This long period of use has indeed generated some alternative sources of data in support of *B. thuringiensis*, especially Btk. Some of these data were in fact considered and discussed in the Proposed Acceptability for Continuing Registration, PACR2006-09, *Re-evaluation of Bacillus thuringiensis*. As noted in PACR2006-09, no increases in health effects were observed during large-scale Btk spray programs conducted in Auckland, New Zealand, southern Vancouver Island, British Columbia, and Seattle, Washington, in 1996, 1999 and 2000, respectively. These data, however, were not considered for the removal of sensitization statements on product labels at the time of re-evaluation. As a result, PMRA has conducted a re-assessment of the sensitization potential of *Bacillus thuringiensis* which considered the detailed rationale provided by the objector.

According to the information and data supplied by the objector, no adverse health effects or respiratory reactions to *B. thuringiensis* were reported in numerous workers exposed to Btk and *B. thuringiensis* subsp. *israelensis* (Bti). In some cases, however, positive skin test reactions and specific IgE and IgG antibodies to spore extracts of *B. thuringiensis* were observed. These observations, according to the objector's rationale, do not necessarily indicate a symptomatic state, but are rather indicative of previous exposure to these microbial organisms. The **petitioner** has also provided a number of published studies which note that, at certain exposure and/or at certain periods of life, exposure to some microorganisms may be beneficial and may even reduce the risk for allergies. Researchers have found that bacterial exposures (particularly Gram-negative bacteria and associated lipopolysaccharide) generally induce Th1 (T helper cell) immune cascade. Th1 immune cascades stimulate the cellular immune system (e.g., macrophages) as opposed to Th2 immune cascades which stimulate the humoral immune system (e.g., B-cells and the production of antibodies). There is also growing evidence suggesting that early childhood exposure to bacteria reduces the incidences of allergies by stimulating a larger population of Th1 cells as opposed to Th2 cells. These findings, however, are not definitive meaning that some individuals can still develop allergies despite early exposure to bacteria. In addition, some

researchers noted that, if B-cells were already primed to produce IgE antibodies, microbial antigens could still stimulate those B-cells and thus exacerbate existing allergic conditions. Also, positive sensitization reactions were reported in several dermal sensitization studies conducted on previously registered and currently registered products (see references below) despite the limitations noted above.

Considering all the available data on *B. thuringiensis* at this time, PMRA has determined that *B. thuringiensis* has some potential to induce sensitizations reactions in previously unsensitized individuals. As a result, all product labels must include the statements, "Potential Sensitizer" and "May cause sensitization." on the principal and secondary display panels.

Studies

PMRA 1381470	2000. Skin Sensitization Study in Guinea Pigs, DACO: M4.6.
PMRA 1193164	Human Health and Safety Testing, Reporting of Hypersensitivity Incidents, Dermal Sensitization Study in Guinea Pigs, Final Report, Completed December 8, 1997
PMRA 1208220	Dermal Sensitization Study of Dipel R6AF in Guinea Pigs (L08151-B), DACO: 4.6.6.
PMRA 1247735	Hypersensitivity Study on Teknar in the Guinea Pig, DACO: 4.6.6.
PMRA1169441	Dermal Sensitization – Guinea Pig, DACO: 4.2.6

Note: These study reports are available in the PMRA Reading Room.

3) Personal Protective Equipment:

The precautionary statements include a statement to 'Avoid breathing dust/spray mist' and a mandatory requirement for a NIOSH-approved '-95' respirator face-mask when handling, applying, or performing cleanups associated with the product. This requirement will provoke a negative response amongst applicators and the public alike.

Given that, as indicated in the PACR document:
' The risk from occupational exposure, however, was determined to be low given the lack of mammalian toxicity." and that "Occupational and non-occupational exposure in Canada is expected to be lower in than in the United States, as the Canadian use rates are generally lower."

And that

'This decision was based on the sum total of all toxicology data submitted to the USEPA along with the lack of any report of significant human health hazards of the various *B. thuringiensis* strains.'
Therefore, the proposed label language is excessively negative and not supported by the available data. The precautionary language and mitigation required is inconsistent with the

potential risk due to exposure. The requirement to have workers exercising this level of precaution sends a message to workers and the public that the material being applied is relatively dangerous since similar precaution is not required of many chemical alternatives. There should be no requirement for a dust mask when friability and other applicable studies indicate negligible potential for exposure to dust and inhalation studies indicate minimal toxicological concern from exposure. While harmonization of Canadian labels with the U. S. for similar products is a worthwhile objective in principle, the policy of requiring dust masks for microbials when testing indicates no apparent risk and no guidelines exist for studies to refute the perceived risk is bad policy on either side of the border.

In most forestry and agricultural application scenarios, liquid Bt formulations are handled via a closed-loop pesticide mixing and loading system; mixers and loaders may not be exposed to the product; consequently the need for a NIOSH -95 filter is not required.

The new label language requiring the use of PPE for all handlers of Bti formulations is unnecessary and poses undue requirements upon registrants and end-users.

It has been stated that based on all available data, current labeled applications pose no risk to applicators, handlers or bystanders; therefore the use of a NIOSH-95 filter is an unwanted restriction not supported by fact.

Not only does this drive up the cost of public health programs, (a significant concern for many large scale municipal programs) it absolutely provides the wrong message to residents of the treated areas. A dust mask for hygiene purposes is adequate protection for Bti handlers. Residents will not easily accept the safety of Bti based products when they are confronted with NIOSH-95 equipped applicators working in their neighborhood.

VBC Proposal: PMRA should propose label language that is supported by data. PMRA recognizes that there are already several strain sources and therefore PMRA should also recognize the variability within these sources for numerous factors, including unique characteristics and usage patterns. The cautionary notes re Sensitization and the requirement for '-95' NIOSH respirators should be left open to being ameliorated based on scientific data.

The current PMRA policy on the requirement of a dust/mist filtering respirator mask (MSH/NIOSH approval number prefix TC-21C) or a NIOSH-approved respirator with any N-95, R-95, P-95 or HE filter for biological products was largely adopted due to hygienic/sensitization concerns associated with the use of large concentrations of micoorganisms as well as harmonization activities such as joint reviews under North American Free Trade Agreement (NAFTA). In some cases, masks/respirators may also be required as a result of acute mammalian testing (i.e., pulmonary studies).

The re-evaluation of *B. thuringiensis* was largely accomplished using previously submitted data as well as the U.S. EPA Reregistration Eligibility Decision (RED) for *B. thuringiensis*. During its review, PMRA accepted the conclusions made by the U.S. EPA as well as the Agency's recommendations (including the standard requirement for respirators/masks). The PMRA has noted the objector's concern with harmonization activities and would like to add that the requirement NIOSH-approved respirator/mask is justified since this microorganism has the potential to induce sensitization reactions and can persist in the lungs if inhaled. Acute pulmonary studies conducted on various *B. thuringiensis*-based products have demonstrated severe effects at high doses (i.e., $\geq 10^8$ colony forming units per animal; see references below). Although these

effects are not expected to occur following a single operational exposure, the observed persistence of *B. thuringiensis* in the lungs could lead to an accumulation of spores in the lungs of applicators, and handlers/mixers through repeated exposure during an entire use season. The above-noted respirators/masks can significantly reduce the accumulation of this microorganism in the lungs of workers in situations where inhalation exposure is likely. The petitioner, however, has noted that the requirement for a respirator/mask is unnecessary if closed transfer systems are used to load the product onto aircrafts. The PMRA has carefully considered this comment and has decided to make the following changes to the aerial application instructions *B. thuringiensis*-based products:

- the handler requirement for a NIOSH-approved respirator/mask and eye goggles may be waived when handlers use closed systems to load *B. thuringiensis*-based products onto aircrafts;

- when reduced personal protective equipment is worn, the respirator/mask and eye goggles must be immediately available for use in the event of an emergency such as a spill or equipment breakdown; and

- as noted in the Re-evaluation Decision Document, RVD2008-18, the requirement for eye goggles may be waived entirely if indicated by eye irritation test data or an acceptable rationale.

As a result, the following aerial application instructions and precautions will be required on all *B. thuringiensis*-based products that have aerial applications:

> "**Aerial Application Instructions:**
> Apply only by fixed-wing or rotary aircraft equipment that has been functionally and operationally calibrated for the atmospheric conditions of the area and the application rates and conditions of this label.
>
> Label rates, conditions and precautions are product-specific. Apply only at the rate recommended for aerial application on this label. Where no rate for aerial application appears for the specific use, this product cannot be applied by any type of aerial equipment.
>
> Ensure uniform application by using appropriate marking devices and/or electronic guidance equipment.
>
> **Use Precautions:**
> Apply only when meteorological conditions at the treatment site allow for complete and even coverage. Apply only when meteorological conditions are in compliance with local and/or provincial authorities.
>
> **Operator Precautions:**
> DO NOT allow the pilot to mix product to be loaded onto the aircraft. However, loading of premixed product with a closed system is permitted. It is desirable that the pilot have communication capabilities at each treatment site at the time of application.
>
> The field crew and the mixer/loaders must wear the personal protective equipment described in the PRECAUTIONS section of this label. When handlers/loaders use closed systems to load the product onto the aircraft, the handler requirement for eye goggles and a NIOSH-approved

respirator/mask with any N-95, R-95, or P-95 filter for biological products may be waived. When reduced personal protective equipment is worn, the respirator/mask and eye goggles must be immediately available for use in an emergency such as a spill or equipment breakdown.

All personnel on the job site must wash hands and face thoroughly before eating and drinking. Protective clothing must be washed before reuse. Decontaminate aircraft cockpits and vehicle cabs if contamination occurs.

Product Precautions:
Read and understand the entire label before opening this product. If you have questions, call the manufacturer at [insert toll free number] or obtain technical advice from the distributor or from your provincial agricultural or forestry representative. Application of this specific product must meet and/or conform to the aerial uses and rates on this label."

For *B. thuringiensis* subsp. *israelensis* (Bti)-based products, handlers, mixers and loaders of commercial and restricted use products are required to wear the listed personal protective equipment. As noted in Re-evaluation Decision Document, RVD2008-18, *Bacillus thuringiensis* subsp. *israelensis* applicators may remove gloves, eye goggles and respirators/masks if the design and delivery of the application apparatus reduces exposure to a negligible level.

With regards to concerns with the cost and the public perception of NIOSH-approved respirators/masks, PMRA is aware of these concerns and would like to note that the Agency's primary concern on this matter is the health and safety of all handlers, mixers/loaders, and applicators. The PMRA would also like to clarify its response to this concern in RVD2008-18 by adding that some NIOSH-approved N-95 masks look almost identical to regular dust masks and are thus not any more intrusive or threatening in appearance.

Studies

PMRA 1174032	Acute Pulmonary Toxicity/Pathogenicity Study of Dipel Technical Material (Bacillus thuringiensis var Kurstaki) in Rats, Final Report, DACO: M4.2.3.
PMRA 1174179	Four-Week Subacute Inhalation Toxicity Study in Guinea Pigs. Dipel. Final Report. Ocotber 17, 1973. DACO: M4.2.3.
PMRA 1381464	1988, Murine Pulmonary Toxicity of Bacillus thuringiensis sp. Microbial Pesticides, DACO: M4.2.3.
PMRA 1465204	1990, Acute Pulmonary Toxicity / Pathogenicity Study of Vectobac Technical Material (Bacillus thuringiensis var. israelensis) in Rats, Document 5, DACO: M4.2.3.
PMRA 1174389	Acute Pulmonary/Pathogenicity Study in Rats, DACO: M4.2.3.

PMRA 1225754 Acute Pulmonary Toxicity and Infectivity to Rats, DACO: 4.2.3, 4.6.3.

4) Label Language - Chemigation

End-use products:

VBC would question the requirement to have all end-use labels include a 'Do not apply by any type of irrigation system.' For certain agricultural Btk uses, chemigation may be an effective way of applying the product. No scientific rational for the statement has been proposed by PMRA.

VBC Proposal: The possibility for this application method should be open to a risk assessment.

The possibility for chemigation is open to a risk assessment; however, appropriate efficacy data, as well as residue and environmental fate data, are required to support registration of chemigation as an application method (Regulatory Directive DIR93-13: *Chemigation*). Any products/uses for which appropriate data are submitted in support of application by chemigation will be subject to evaluation and risk assessments. If the results of the evaluation and risk assessments are acceptable, the statement in question may be removed from the label and replaced with appropriate use directions.