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Turning Research on Microbial Bioherbicides into Commercial Products – A *Phoma* Story

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ABSTRACT

The literature cites many claims of potential new bioherbicides based on isolate screening and biological assessment. However, only 8.1% have achieved verifiable commercial success, 19.4% uncertain (i.e. registered but not commercialized), and 72.5% have been ineffective. To get more bioherbicides to the marketplace there must be a better partnership between business and science in order to strengthen the research supporting commercialization. This paper describes how a bioherbicide innovation chain (research model) has been merged with the stage and gate process (business model) to develop *Phoma macrostoma* for broadleaved weed control. Prior to industry involvement, research concentrated on discovery and proof-of-concept by characterizing the fungus, evaluating fermentation requirements, demonstrating efficacy and environmental safety, learning the mode of action, and studying the economics and market potential. The inclusion of industry to assist with technology assessment and product development brought new perspectives and defined key decision points that would either let the project proceed or stop it completely. Key issues were: economically feasible fermentation process; consistent and high efficacy; long shelf life stability; safety to mammals and the environment. Presently, *P. macrostoma* is in the latter stages of pre-commercialization completing the pilot scale manufacturing process and waiting for the regulatory decisions in anticipation of a product launch.

Keywords: microbial products, biological control, commercialization, broadleaved weed control, *Phoma macrostoma*

INTRODUCTION

Bioherbicides are being developed around the world as "green products" from nature that will control or suppress weed populations without causing harm to desirable plants. These natural herbicides are typically comprised of two components: a living organism, such as a fungus, bacterium, or virus and their natural substances produced during their growth (i.e. enzymes, phytotoxins, elicitors, secondary metabolites). They are mass produced and formulated to be applied as granules, dusts, or sprays in a fashion similar to synthetic herbicides. Despite the similarities in formulation and application, there are significant differences between bioherbicides and synthetic herbicides, including their origins (biological vs chemical), modes of action (multiple vs singular), manufacturing methods (fermentation vs synthesis), longevity of shelf life and stability (short vs long), and in the complexity of biological interactions with the hosts, nontargets, and environment (Bailey 2004).

The concept of bioherbicides evolved in the 1970s when researchers in the United States discovered that *Phytophthora palmivora* Butler killed strangler vine (Burnett *et al*. 1973) and *Colletotrichum gloeosporioides* (Penz.) Sacc. f. sp. a*eschynomene* killed northern jointvetch (Daniel *et al*. 1973). By the 1980s, these fungi had been registered and commercialized as DeVine® and Collego™, respectively (Bowers 1986; Kenney 1986). By the year 2000, there were eight bioherbicides registered and/or commercially available worldwide and more than 50 pathogen – weed combinations reported as potential opportunities of bioherbicides under development (Charudattan 2001). The interest in bioherbicide research has remained consistent as there were 509 papers published from 1987 to 2009 (rate of 23 papers per year) that mentioned bioherbicides or mycoherbicides (Ash 2010).

Ash (2010) points out that if success in biopesticide research is considered to be registration and commercialization, then the success rate is low. Charudattan (2005) defined a bioherbicide as a "verifiable success" when it was registered, commercialized, and used with some regularity. Bioherbicides that were registered but not commercialized for various reasons are not considered successful. Charudattan (2005) concluded that there have been only five verifiable successes: *Colletotrichum gloeosporioides* f.sp *aeschynomene* for control of northern jointvetch, *Chondrostereum purpureum* (Per.:Fr.) Pouzar for control of weedy tree species, *Phytophthora palmivora* for control of strangler vine, *Xanthomonas campestris* Migula pv. *poae* for control of annual bluegrass, and *Acremionium* sp. for control of scrambled egg bush. More recently, the bioherbicide made from *Sclerotinia minor* Jagger has been registered and sold in Canada for broadleaved weed control in turfgrass (Bailey 2010). When comparing the rate of success to the total number of projects, only 8.1% were verifiable successes, 19.4% were uncertain (i.e. registered but not commercialized), and 72.5% were ineffective (Charudattan 2005; Ash 2010). By comparison, a survey of six leading crop protection companies showed that between 2005-2008 the average number of compounds synthesized and screened as crop protection products was 140,000, but only 1.3 were advanced to development and only 1 was registered (CropLife International 2010). In 1995, the average number of products screened was 52,500, four went into development and only one was registered. The study suggested that this change reflected an increased difficulty in finding new product leads and also greater caution towards rising financial costs resulting in product development not justifying the potential return. It was estimated that the costs of discovery and development of synthetic compounds between these two study periods rose from $152 M USD to $256M

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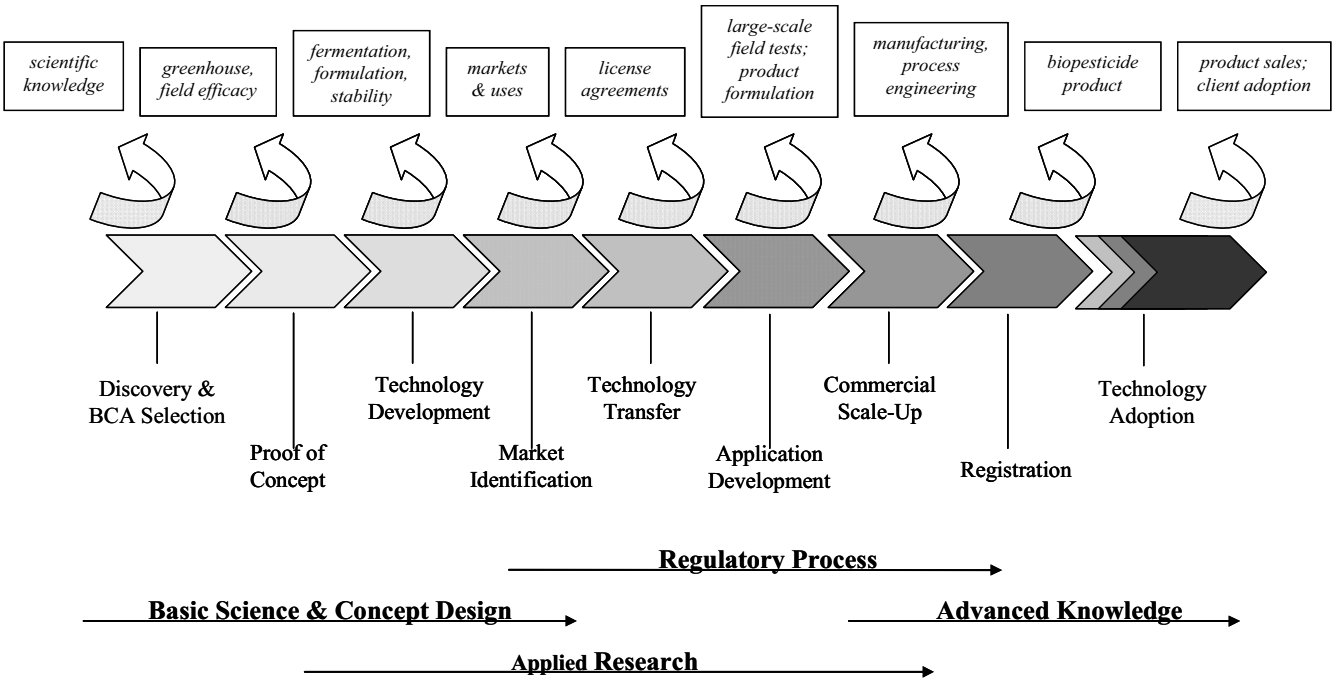

Fig. 1 The bioherbicide innovation chain. Reprinted from Bailey *et al.* (2009) with permission of M. Rai (Ed) *Advances in Fungal Biotechnology*, IK International Publishing House Pvt. Ltd.

USD. In contrast, the cost of developing a biopesticide is $3-5 M USD (Bailey 2010).

The present challenge for researchers and industry is to find a way to increase the number of successes by increasing bioherbicide product commercialization. From the research perspective, the challenges have exclusively focused on the aspects of science as they relate to what makes a good biocontrol agent and the biological, environmental, and technological limitations of the systems (Auld and Morin 1995; Charudattan 2005; Hallett 2005; Bailey and Mupondwa 2006; Rosskopf 2007; Ash 2010). From an industry perspective, the major limitations and challenges arise from issues related to target selection, efficacy, mass production, and cost of production, intellectual property, market economics, regulations, and product adoption (Cross and Polonenko 1996; Bailey and Mupondwa 2006; Bailey *et al*. 2009; Ash 2010). To get more bioherbicides to the marketplace, there has to be a better partnership between business and science (Fravel 2005). This paper presents a bioherbicide research and development model that can be used to transition between research and business requirements. It also illustrates how the model was used to develop the bioherbicide *P. macrostoma* Montagne for broadleaved weed control.

BIOHERBICIDE RESEARCH AND PRODUCT DEVELOPMENT MODELS

There are many claims in the literature of potential new bioherbicides based on isolate screening and their biological assessments (Charudattan 2001; Ash 2010). Research may continue on these pathogen-weed systems for better understanding of the virulence of the biocontrol agent; weed population structure and genetic diversity; host morphology and interaction with the biocontrol agent; genetic modification of the biocontrol agent; ecological presence and role in environment; growth parameters and environmental influences on the biocontrol agent; biological and molecular characterization for taxonomic identification, and impact on nontargets (Charudattan 2005; Boyetchko and Rosskopf 2006; Ash 2010). Applied research focuses on fermentation and mass production at a lab scale, formulation, and application technologies that can be used with the bioherbicide candidates. Unfortunately, many of these candidates are not suitable for commercialization, yet the research on them continues. There are usually no critical decision points integrated within the research process that forces an analysis of whether the potential candidate is really suitable from a business perspective. Cooper *et al.* (2002) wrote that "much fundamental research is undirected, unfocused, and unproductive." Lidert (2001) blamed the scarcity of bioherbicides in the marketplace on researchers at universities and public institutions whose projects lacked clarity of purpose meaning that they concentrated on only the science and producing publications to the exclusion of bringing a product to market. As a consequence, he described five key areas that are crucial to commercial success but in which most bioherbicide projects are deficient: 1) exaggerated confidence in the environmental drivers of the market; 2) product concepts not clearly defined with knowledge of end users' needs, registration requirements, and competitive forces; 3) simplistic views on positioning and market strategy; 4) underestimation of registration costs and other hurdles; and 5) insufficient cost performance (i.e. cost of developing the product is high relative to the commercial return) and inadequate shelf stability. Conversely, those bioherbicides that have become verifiable successes have managed to address these barriers to commercialization in one way or another. For example, *Sclerotinia minor* did not have exaggerated confidence in the environmental drivers in the market because herbicides were banned under municipal and provincial legislation in Canada before alternate weed control strategies became available in the market place thus creating both a public/consumer demand and development opportunity. *Chondrostereum purpureum* fit a niche market in Canada where by mass aerial spraying or mass cutting of weedy tree species was frowned upon by government and public due to the harm caused to local desirable species, yet power companies had to keep the power lines clear of the trees, so the bioherbicide which is a paste that is painted on the weedy stumps was an environmentally acceptable option.

In an attempt to overcome these deficiencies, a bioherbicide innovation chain was created by a team of bioherbicide researchers (Bailey *et al*. 2009). The chain (**Fig. 1**) relies on a lead researcher to collaborate with individuals possessing complementary knowledge and skills to move through nine stages from discovery and selection, proof-of-concept, technology development, market identification, technology transfer, application development, commercial

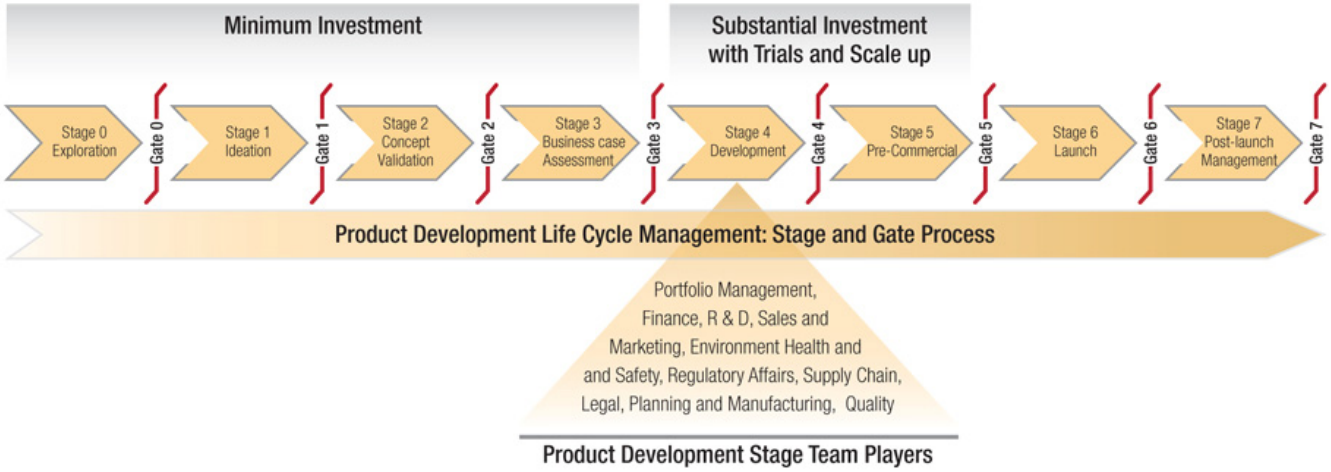

Fig. 2 The Scotts Company's stage and gate process uses a skilled team to develop a bioherbicide.

scale-up, registration, and technology adoption. The research plan combines both basic and applied research using regulatory guidelines for registration to determine what scientific information must be collected (PMRA 2001). Bailey *et al.* (2009) and Bailey (2010) explained the model in greater detail outlining the types of research and collaborations that are needed to move the project through the nine stages. In this model, science is the primary driver at nearly all the stages, although considerations are also given to regulatory issues, intellectual property protection, market analysis, and technology transfer.

Industry takes a slightly different approach to product development, using a "stage and gate" process that divides the project into distinct stages that are separated by management decision gates. The first Stage-Gate® model was developed in 1986 and was broadly adopted by a number of different types of businesses to help them keep focused on the product development chain in order to move as quickly as possible to product launch (Cooper 1986). Later the Stage-Gate TD (Technology Development) model evolved for science projects where the immediate deliverable may be a product or knowledge or capability leading to a new product in the future (Cooper *et al.* 2002). This model features a discovery/idea component, as well as technical assessment and then detailed investigation; the decision criteria used with the technology development model are often more strategic at many of the stages and less financially dependent.

The stage and gate process developed by The Scotts Company for their new Naturals line of pest control products identified seven stages: ideation, concept validation, business case assessment, development, pre-commercialization, launch, and post launch management (**Fig. 2**). It employs cross-functional teams drawing people from research and development, regulatory affairs, sales and marketing, finance, quality control, manufacturing logistics, supply chain, legal, environmental safety and health, and portfolio management to complete prescribed tasks at each stage prior to obtaining management approval to proceed to the next step. In this model, science is not the primary driver and the process allows for the injection of objective views from closely related fields that minimize the deficiencies noted by Lidert (2001).

A CASE STUDY: *PHOMA MACROSTOMA* FOR BROADLEAVED WEED CONTROL

Phoma macrostoma is a fungus that was isolated from Canada thistle (*Cirsium arvense* L. (Scop.)) plants in Canada and has demonstrated the ability to cause severe chlorosis and bleaching of leaf tissues resulting in eventual death to several economically important broadleaved weeds without harming monocotolydenous plants (Bailey and Derby 2001). The technology was first discovered and initially developed through the proof-of-concept stage by Agriculture & Agri-Food Canada, Saskatoon. Subsequently an industry partner was sought to assist with product development leading to commercialization which was carried out in collaboration with The Scotts Company, Marysville, Ohio. This case study shows how the bioherbicide innovation chain (research model) and the stage and gate process (business model) were merged to guide the science behind the technology from discovery to product launch.

Phoma 1996-2002: Discovery and proof of concept

Between 1985 and 1994, field surveys collected Canada thistle plants from across Canada to isolate fungi from the leaves and roots. Several morphologically similar isolates were purified and tested to verify Koch' postulates demonstrating that these isolates were the causal agent of leaf lesions on Canada thistle, but despite the initiation of disease symptoms the fungus did not cause extensive enough damage to kill the host. Prior to discarding the pathogen due to inferior disease development, the screening procedures were changed to examine the effects when the fungus was applied to soil. Using an inoculum mat bioassay, which inverts a colonized agar plate onto soil containing roots of Canada thistle, the emerging plants came up white and the root growth was inhibited eventually leading to plant death (Bailey and Derby 2001). Accidental dispersal of dandelion seed to the inoculated thistle pots resulted in dandelions emerging white and then dying. The fungal isolates were identified as *P. macrostoma*, thus completing the agent selection stage. The selection stage was partially serendipitous but it was also based on the creativity to examine the same problem from different perspectives. If the only viewpoint was that a leaf pathogen has to be re-applied to the leaves to cause damage then *P. macrostoma* would not exist as a bioherbicide because the resultant damage was insignificant. It was only when a different perspective was taken (i.e. the application of the leaf pathogen to soil) was the full extent of the damage realized. Therefore, new opportunities may arise from nontraditional approaches.

The discovery and proof-of-concept stage was not complete until additional scientific knowledge was acquired on host range, efficacy, environmental fate and mode of action. Extensive host range testing showed that many dicotyledonous plants showed the same symptoms as described above when *P. macrostoma* was applied to the soil, but monocotyledonous plants were tolerant and showed no symptoms (Bailey and Derby 2001). For example, wheat (*Triticum aestivum* L.), barley (*Hordeum vulgare* L.), oat (*Avena sativum* L.), millet (*Panicum miliaceum* L.), canary seed (*Phalaris canariensis* L.), and various grass species (*Poa pratensis* L., *Lolium perenne* L., *Lolium multiflorum* L., *Festuca*

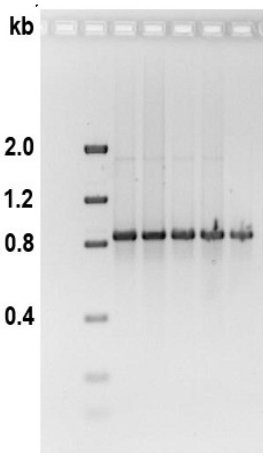

Fig. 3 Primer-mediated identification method developed by Zhou *et al.* (2004) shows amplification of an 853 bp fragment, indicative of bioherbicide activity.

rubra L., *Festuca arundinacea* L., *Agrostis palustris* L., *Bromus inermis* L., *Bromus biebersteinii* L., *Phleum pratense* L., and *Cynodon dactylon* L. were tolerant and the weeds green foxtail (*Setaria viridis* L.) and wild oat (*Avena fatua* L.) were also tolerant. Susceptible weeds included Canada thistle (*C. arvense*), dandelion (*Taraxacum officinale* Weber ex F.H. Wigg.), clover (*Trifolium repens* L.), creeping Charlie (*Glechoma hederacea* L.), plantain (*Plantago major* L.), and ragweed (*Ambrosia artemisiifolia* L.); susceptible crops were canola (*Brassica rapa* L.), mustard (*Brassica juncea* L.), pea (*Pisum sativum* L.) and lentil (*Lens culinaris* Medik.). Tests for efficacy and environmental fate were conducted in the greenhouse and field (Zhou *et al*. 2004). A DNA-specific probe complemented traditional colonization studies to monitor the release of *P. macrostoma* in soil and plant tissues over space and time (**Fig. 3**). At the same time, dose response curves were developed for efficacy against dandelion. These studies showed that *P. macrostoma* effectively reduced dandelion by 80-100% depending on the dose. The fungus did not move away from the site of placement nor did it persist in plant tissues or soil. The other significant discovery was the isolation and characterization of a family of novel phytotoxic metabolites named macrocidins that were produced by the fungus and were responsible for the observed symptoms (Graupner *et al*. 2003, 2006). There are several derivatives of macrocidins that show activity but their synthesis is very complex (Bailey *et al*. 2009). The mode of action of macrocidins remains unknown.

Concurrently, a market analysis was conducted to explore the potential fields of use (i.e. agriculture, horticulture, agro-forestry), the need for a new product in these fields, market size, and market demand. These studies indicated there was commercial potential and so in 2001 patent protection was sought and a PCT (Patent Co-operation Treaty) application filed the next year expanded the protection to seven countries. A competitive process was initiated which culminated in 2003 with the selection of The Scotts Company as the industry partner to collaborate with Agriculture & Agri-Food Canada on technology and product development, thus giving the company the first right to license a bioherbicide for commercialization.

The work in this time period was mainly research driven following the biopesticide innovation chain for discovery of basic scientific information about the fungal species, selection of the specific isolate, proof-of-concept demonstrating field efficacy and environmental safety, and preliminary research on fermentation technology (**Fig. 1**). During this stage, an economic analysis was introduced to validate potential markets and identify future product uses. The team comprised scientists in the fields of plant pathology, chemistry, and economics. It was not until the team was joined by industry that the stage and gate process became forefront and the team was gradually expanded over the developmental period to having representation from science (research and development) as well as finance, marketing, regulatory affairs, legal, quality assurance, environmental health and safety, manufacturing, supply chain organization, and overall portfolio management.

Phoma 2003-2010: Technology assessment and product development

Once the collaboration between AAFC and The Scotts Company was initiated, it took seven years to work through Stages 2, 3, and 4 of the stage and gate process and the team grew exponentially (**Fig. 2**). Work plans were drawn showing what activities were associated with specific team members and clearly defining decision points indicating either a "Go Ahead" or "No Go" through the various gates.

In Stage 2, the marketing members defined what claims the company would want to make to consumers. This permitted the research members to design tests over a number of stages to collect evidence in support of the claims. The regulatory affairs members provided advice to the research members on the type of data that would likely be required for registration. Over the next few years, the research members collated the information from the published literature and the data from ongoing studies into a formal pre-submission consultation with the Pest Management Regulatory Agency (PMRA) in Canada and the Environmental Protection Agency (EPA) in the USA in 2007; this step defined the remaining gaps in the research that needed to be closed before submitting a regulatory data submission package for joint review by both countries. This stage addressed gaps such as survival of the fungus in water, determining if the bioherbicide activity was leached from soil, and genetic characterization of the isolate. One study showed that mycelial propagules lost viability over time when immersed in water (about 1 log unit per 28 days) which reduced the risk of *P. macrostoma* causing contamination of neighbouring water bodies (unpublished). Another study simulated various amounts of rainfall applied to three soil types treated with *P. macrostoma* showing that 80% of the macrocidins were released after receiving 75 mm of water (Bailey *et al*. 2010b). Clay soils retained more bioherbicidal activity than sandy soils.This study demonstrated that when the bioherbicide is applied to soils at field capacity or drier the bioactivity is localized and poses little risk of harming non-target plants. Molecular characterization of the bioherbicide isolate was compared to other bioherbicidal isolate of *P. macrostoma*, non bioherbicidal isolates of *P. macrostoma*, and also other *Phoma* species using a variety of techniques such as randomly amplified polymorphic DNA, pulse field gel electrophoresis, and amplified length fragment length polymorphisms (Pitt *et al*. 2005; Zhou *et al*. 2005). The data showed that considerable diversity exits within the species *P. macrostoma*. The bioherbicidal isolates are highly related to each other appearing to be clones with two biotypes occurring in the ecozones across Canada (**Fig. 4**), thus posing minimal risk of exchanging new genetic information from one part of the country to another.

By Stage 3, research concentrated on understanding how the fermentation and formulation of *P. macrostoma* was influenced by its biology and mode of action. It was only after we understood these factors that the first generation product was defined as being a granular formulation produced via solid substrate fermentation. This was a key decision point and was scrutinized very closely. Submerged fermentation has been the industry standard in North America for most microbial products. But with *P. macrostoma*, the advances made in producing more efficacious and viable end products were clearly slower using liquid fermentation than with solid state culture. *P. macrostoma* retained close to its original viability for at least one year (i.e. within a half a log unit) and only lost 1.0-1.5 log units from the original counts after two to three years giving it a very sta-

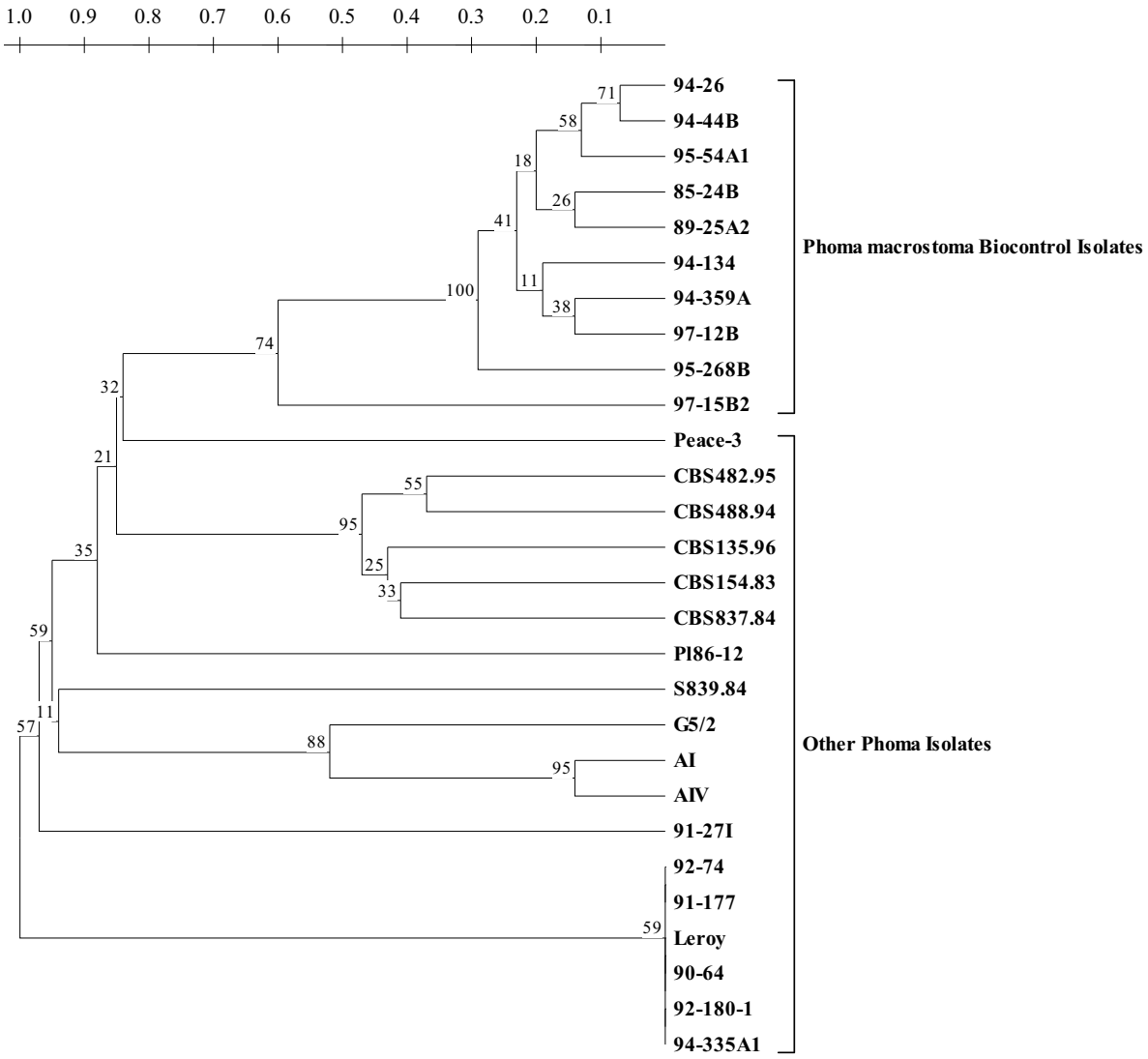

Fig. 4 Phylogenetic relationship among 10 bioherbicidal isolates of *Phoma macrostoma* and 18 reference species in the genus *Phoma* analyzed using randomly amplified polymorphic DNA data (published in Zhou *et al*. 2005). The biocontrol isolates were clustered together and genetically distant from the reference isolates. Within the cluster of biocontrol isolates, the isolates originating from two different Canadian ecozones were randomly scattered. The evolutionary distance scale was placed on the top of the figure and a bootstrap value was presented on each node of the tree.

ble, long shelf life when stored dry at room temperature. Formulation studies examined the effect of particle size, the addition of adjuvants, and granule disintegration on the viability and release of *P. macrostoma* as well as the effects of these factors on efficacy (Bailey *et al*. 2010a). The results showed that smaller granules resulted in greater efficacy and that the addition of Tween 60 to the formulated granule or reducing the sphaeronization speed resulted in faster disintegration of the granules which in turn resulted in better efficacy. After the production decisions were made, the financial team considered the potential market size, special market opportunities, how the new product would fit with other existing products within the company and whether it might cannibalize one of their existing products.

Stage 4 required considerable capital investment in time, personnel and money from the finance members in order to conduct efficacy testing from coast to coast, finalizing the lowest effective rate of application, verifying crop tolerance, scale up the fermentation and formulation processes, and conduct third party toxicology studies conducted under certified good laboratory practices. At this stage other people were introduced to consider the supply chain logistics and how the final product would move within the company and to distributors. Marketing and sales people started to project how to market the product to consumers and conducted focus groups to test the consumers' responses. But, the regulatory affairs members had the largest role in coordinating others from research, environmental safety and health, and marketing to process years of data and write reports to support all claims and fulfill the regulatory requirements previously outlined by the federal regulatory agencies in Canada and the USA. The data registration package was submitted in November 2009. Now the timelines to reaching a product launch became critical, and a portfolio manager was needed to keep everyone focused on working to get a final product out in the marketplace in the shortest time possible.

It is important to note that the success of moving through Gates 2-4 was due to maintaining an integrated and highly communicative team comprised of members from both AAFC and The Scotts Company with each partner providing complementary skills to the project.

But it was ultimately the responsibility of the research members to deliver crucial scientific evidence in order to move past the key decision points which would allow the project to proceed on to the next stage (or close the gate immediately). The key decision points for this project were: i) development of rapid assays that were highly correlated to field results, ii) biological characterization of the fungal isolate to support its identification and general safety under various conditions, iii) development of an economically feasible fermentation process, iv) verification of broad spectrum efficacy and crop tolerance under different environments, iv) optimization of the formulation for ap-

Table 1 Dandelion control (%) at 28, 56, and 84 days after application (DAA) of *Phoma macrostoma* as a pre-emergent bioherbicide in Guelph, ON.

Rate of application	% Dandelion control at 28 DAA	% Dandelion control at 56 DAA	% Dandelion control at 84 DAA
1X	83 a*	92 a	92 a
1/2 X	76 ab	72 ab	76 ab
1/4 X	51 bc	52 bc	52 bc
1/8 X	48 c	26 cd	41 c
0 X	0 d	0 d	0 d

* Different letters within a column indicate significant differences according to a Duncan's Multiple Range test, P=0.05.

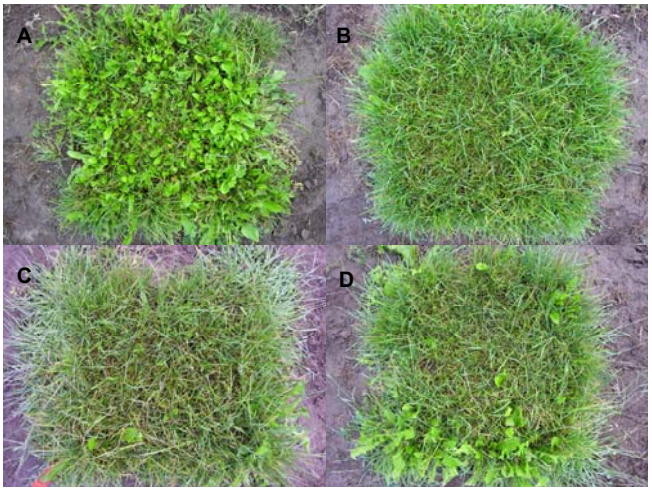

Fig. 5 Efficacy of pre-emergent applications of *Phoma macrostoma* compared to the untreated control (A) and the hand-weeded control (B). The rates of bioherbicide application were 1X (C) and 1/2X (D) the standard field rate.

plication, shelf life and efficacy, v) completion and clearance of Tier 1 Chronics and Tier 1 Environmental toxicology tests, and vi) pilot scale feasibility and economics.

The main features that made *P. macrostoma* attractive for product development were market potential, broad spectrum weed control, high efficacy, long shelf life, and low risks to environment and health. Market potential for *P. macrostoma* was determined to be very broad, as the research proved it could provide broad spectrum weed control in turfgrass, agriculture, and agro-forestry situations on a global scale. Two application strategies were developed using a granular formulation; pre-emergent applications for controlling weed seed banks and post-emergent applications for controlling established weeds. A decision was made to concentrate efforts on the turfgrass (non food) market first since this was the core business of the company. To illustrate marketing claims that the bioherbicide has broad spectrum weed control and is safe to turf grass, data had to be collected on efficacy for each specific weed (dandelion, Canada thistle, plantain, clover, etc.) and the tolerance of various grass species to *P. macrostoma* at a minimum of four rates (i.e. 0X, ½X, 1X, 2X) in at least five tests in several locations from coast to coast. Over the seven years, there were 129 efficacy trials and 69 phytotoxicity trials conducted in eight provinces in Canada and four states in the USA. Crop tolerance was demonstrated on 10 grass species as well as several turf grass mixtures. Efficacy data was generated on 14 weed species. A high level of efficacy (greater than 80% weed control) was obtained in more than 50% of the trials with pre-emergent applications controlling dandelion, clover, plantain, scentless chamomile, English daisy, chickweed, wild mustard, and ragweed when the application rate was optimized for each species (**Table 1, Fig. 5**). Overall, host range testing on weeds and desirable ornamental and food crops evaluated the responses to 35 plant families. The results showed that *P. macrostoma* caused injury (photobleaching and mortality) in 52 plant species but caused no injury to 48 plant species. Highly injured plants came mostly from the *Asteraceae*, *Brassicaceae* and *Leguminosae*. Through judicious use patterns, such as applying *P. macrostoma* to control broadleaved weeds in turfgrass or in cereal crops, the targeted weeds would be harmed but the tolerant crops would be safe. Previous research had already demonstrated that persistence from one year to the next would not be an issue which further substantiated environmental safety. Mammalian toxicology and ecotoxicology studies conducted according to PMRA and EPA standards confirmed that *P. macrostoma* showed no signs of toxicity or pathogenicity in rats, rabbits, birds, fish, arthropods and other invertebrates.

Phoma 2011-2013: Commercialization and launch

The final series of stages to address are in progress since *P. macrostoma* is still under regulatory evaluation as of the end of 2010. Pre-commercial development which is the focus of Stage 5 ensures that the commercial manufacturing process will deliver a product that works as expected. Research will continue with field testing to confirm efficacy and product claims, and quality control will evaluate shelf life and product purity of materials produced using the commercial manufacturing process. Sales and marketing will finalize the labels and art work for the packaging. Regulatory affairs will double check the science behind the labels and claims and initiate state registrations in the USA. Detailed schedules will be made by the supply chain, portfolio management and manufacturing members for target production and shipping dates and presentations will also be made to retailers showing them how to get the best shelf space for consumers to see the product. Time will be spent on training the sales force and creating an education plan for the end users. Launching the product is the focus of Stage 6 which cannot proceed until the registration has been received and sufficient product volumes can be manufactured and distributed to cover the test market region. Stage 7 actually restarts the stage and gate process again by bringing back the research members to look for continuous improvements in product efficacy, lowering costs of manufacturing, collecting data for new claims and label expansion. The sales and marketing members track the product distribution and point of sales and develop new claims depending on what evolves from new research. And so the product development life cycle begins again. Key decision points at these stages are to successfully obtain the federal and state Registrations, monitor sales and consumer acceptance, and determine if future improvements will increase sales and adoption. The next few years will tell whether *P. macrostoma* becomes a "verifiable success".

CONCLUSIONS

To quote Ash (2010), "… the future of bioherbicides rests with greater collaboration between a wide variety of scientific disciplines and the early and continued input of industry in the process from selecting the correct agent, target weed through to the selection of the business model." In the case with *P. macrostoma*, the relatively early and continued input by industry was a critical component to advancing through product development. The bioherbicide innovation chain requires the researchers to initially focus on understanding the biology of the microorganism thoroughly while keeping in mind some of the key decision points that could be raised by a future industry partner. The inclusion of industry to the project quickly set the key decision points so that together AAFC and The Scotts Company remained focused on the details required to move through the stage and gate process.

The question remaining is whether the template used to develop *P. macrostoma* would be broadly applicable to other bioherbicide projects? Lidert (2001) indicated that not all bioherbicide projects make commercial successes. But

those that do will come from having the research focusing on market segments that favor bioherbicide use, allowing commercial feasibility to guide the research, involving market experts in the decision making, and getting early involvement from a trusted industry partner. All of these factors came together with the *Phoma* project. Another key point was completing a thorough and detailed proof-of-concept that followed the key issues outlined in the microbial registration guidelines; the information provided to the industry partner allowed them to see how the concepts could fit into their market segment and define commercial potential and limitations. If we look at another bioherbicide candidate that was used during the evolution of the bioherbicide innovation chain, *Alternaria cirsinoxia* (Simmons & Mortensen) was thoroughly investigated up to the proof-of-concept stage for control of Canada thistle, but it was decided at the end of that stage that the candidate was not suitable for further product development (Bailey 2004). So in two cases, the overall template served to determine whether the projects should proceed or be halted. For ongoing and future biopesticide projects, the bioherbicide innovation chain and the stage and gate model are being used within Agriculture & Agri-Food Canada and The Scotts Company. Therefore, merging the research and business product development models as described in this paper gives a detailed pathway for other researchers to consider when starting new bioherbicide projects.

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