Challenges of Developing Natural Product-producing Biopesticides

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Marrone Bio Innovations, Inc. Overview

Company Highlights

- Founded April 2006 in Davis, CA
- 3 commercial products, 1 add’l approved, 2 add’l submitted for EPA approval
- Library of 19,000 proprietary microorganisms
- 110+ employees (19 Ph.D.; 67 in R&D)
- Strategic investors: DSM, Syngenta, Mitsui
- Building fermentation facility in Bangor, MI
- Doubling revenues 2012 to 2013
- Listed on NASDAQ as MBII August 2, 2013

Marquee Partners / Distributors

- syngenta
- FMC
- Scotts
- HELENA
- CNI
- IAP
- Simplot
- Crop Production Services
- ENAGE AGRO
- WILBUR-ELLIS

Robust Pipeline

- Opportune™ bioherbicide EPA approved
- Venerate™ bioinsecticide and MBI-011 bioherbicide submitted for EPA approval
- Nematicides, additional herbicides, and plant health products in development
- More than 200 patents issued and pending

Commercial Products Today

- REGALIA
- GRANDEVO
- ZEQUANOX

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Getting a Product to the U.S. Market

**In-house and In-Licensing**

- Discovery
- Pre-Development
- Development

**EPA Review**

1.5 Years (~$1.5M)

- Collection/isolation
- Fermentation proprietary media
- Testing/screening
- Natural product chemistry
- Initial toxicity
- Microbial ID
- File patent
- Gene sequencing
- Processes
- Formulation
- Field test
- Toxicology
- More patents
- 5-batch analysis
- Analytical methods

**Targeted Launch**

2 Years (~$3M)

- EPA submission
- International field trials
- Process & Formulation Optimization
- Mfg scale-up
- QC methods
- Manufacturing
- Packaging
- Labels
- Marketing
- Targeted launch
- National launch
- International expansion
- Crop and target expansion

**Full Launch**

Add 2-5 years for other countries and additional $2-5 million USD
Case Study: REGALIA® Biofungicide

- Extract of giant knotweed, foliar or soil applied
- Ethanol extraction of several compounds containing plant material provides formulation challenges (separation is not a viable path)
- Knotweed supply chain development was difficult and took years to work out
- Regulatory agencies ex-USA required additional compound characterization & toxicology
- Analytical methods required for detection and quantification of several compounds
Case Study - GRANDEVO® Bioinsecticide

- *Chromobacterium subtsgae* (USDA discovery)

- Filed patents on insecticidal compounds produced by the bacteria – different chemical classes each have different mode of action

- NO contact activity (will not kill insects if applied to the cuticle)

- Repellency, feeding cessation, effects on reproduction – huge challenge for assessing efficacy and for development into a product
Mean Number of Aphid Progeny on Treated Leaf Discs

- dH2O (-):
- DF2 3%:
- MBI 203 TGAi 3%:
- Abamectin 10%:

[Bar chart showing the mean number of aphid progeny for each treatment]
Effect of Grandevo® (MBI-203) on Potato Psyllid Egg Laying

![Bar graph showing the effect of Grandevo® on potato psyllid egg laying. The graph compares the mean number of eggs laid by females on different days with and without Grandevo®. The x-axis represents the days (3, 4, 5, 6, 7, 10), and the y-axis represents the mean number of eggs laid per 4 females. The bars show a decrease in egg laying on days 6, 7, and 10 with the application of Grandevo® compared to the control.]
Insects are highly agitated after exposure to GRANDEVO®

USDA-ARS - Tracy Leskey, et al
Horizontal Distance Moved after 0.5 to 4.5 hrs
GRANDEVO® vs. Brown Marmorated Stink Bug

Lethality – Tarsal Contact
USDA-ARS - Tracy Leskey, et al

Time-Phased BMSB Condition
4.5-Hour Exposure Period In Glass Arenas
MBI-203 @ 5.0% (v/v) in Water

%DEAD

%ALIVE

Days After Exposure

Days After Exposure

%Adult BMSB/Category

%Alive

%Affected

%Moribund

%Dead
Case Study - VENERATE™ Bioinsecticide

• New patent pending bacterial species of *Burkholderia rinojensis sp. nov.*,
  – No relationship to pathogenic *Burkholderia* species
  – Discovered in MBI’s discovery screen; isolated from soil collected by MBI employee

• Several patent pending active compounds, different chemical classes, some novel, produced by the bacteria

• Active on contact and by ingestion; broad spectrum—sucking and chewing insects, mites, and flies

• Nontoxic and nonpathogenic to all non-target organisms; slight activity on predatory mites in the lab

• Submission as a microbial to the US EPA
Contact Efficacy Against Lepidoptera Larvae

Photographs illustrating the effects of A396 treatments on BAW. (A) Stunted larva compared to normally developing larva; (B) Larva with liquefied frass; (C) Larva with molting problems; (D) Larva with molting problems (left) compared to control larva.

Appears to affect molting and melanization of the cuticle; also will kill by ingestion.
Contact Efficacy Against Cabbage Looper

- Contact assay: using fractions obtained from the fractionation of crude extract
- Place 1 uL of sample on thorax of 3rd instar larvae

Mortality, CL contact assay with fractions

![Graph showing mortality over days for different fractions and crude extract.](image-url)
Case Study - VENERATE™ vs. Grandevo® Bioinsecticide

- Venerate™ contact activity makes it easier to evaluate than Grandevo® because most chemicals are contact active.
- Grandevo® is more challenging to evaluate because of its complex, non-contact mode of action.
- Venerate™ is not ‘better’ than Grandevo®, just different modes of action. Field efficacy and spectrum are quite similar.
- Plethora of compounds produced by both microbes provides large challenges in fermentation and formulation development – which compounds are most important to optimize?
- What compounds do you use as ‘marker’ compounds for QC in manufacturing?
- Tox testing requires that TGAl (‘technical grade active ingredient’) captures levels of compounds expected in the final product.
Rapidly Spreading Invasive Species

Economic & Ecological Destruction

Marrone’s Solution (molluscicide)
Case Study - ZEQUANOX® for Invasive Mussels

• Derived from soil microbe (*Pseudomonas fluorescens*) discovered by NYSM
  – Composed of 100% dead cells
• Controls mussels in all life stages
  – Perceived as food source—destroys the mussel’s digestive system after 6 hour treatment
• Highly selective toward zebra/quagga mussels
• Effective in a broad range of water conditions and temperatures
• Noncorrosive and nonvolatile
Case Study - ZEQUANOX® for Invasive Mussels

- *Pseudomonas fluorescens* strain has particular, atypical nutritional requirements
- Active mussel-killing compounds are proteins in the cells that rapidly biodegrade after 1 hour of large scale mixing
- Lab jar assays did not mimic in-pipe results
- Using live mussel jar assay for fermentation and formulation development is very slow and difficult
Lessons Learned

• Many very good biopesticides are not selected for development because they do not work in familiar ways like chemical pesticides

• Developing bioassays that address the mode of action is critical

• Consultants and cooperators must use appropriate protocols and take evaluations beyond dead insect counts (plant damage, yields, quality)

• Training of end users in proper timing and use – set expectations, e.g., Grandevo is not a rescue treatment and should not be used alone when there are high insect populations – partner with oil, Oroboost, or other adjuvant
QUESTIONS?

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