

MICROBIAL BIOPESTICIDES: A key role in the multinational portfolio

While there is increasing support for more biological solutions as alternatives to chemical pesticides in both organic farming and IPM systems, the development and commercial success of biologicals has been more difficult because of the size of the companies involved and the fact it is a young, relatively undeveloped market. Among biologicals, microbial (microorganisms), which mainly include beneficial fungi, bacteria, viruses, as well as yeasts, represent the market where probably the biggest number of companies are active and where the Multinational crop protection companies have focused their efforts through partnerships and acquisitions. In 2005, only 26 microbial products for biological disease control with proven effects were marketed by commercial companies in the U.S. market. In Europe, 14 microbial products for disease control were registered and listed on Annex 1 of the Directive 91/414 EEC when we wrote our first article on microbials back in 2010. This was already tremendous progress compared to 10 years before when only one microbial substance, *Paecilomyces fumosoroseus* (fungal bioinsecticide), was listed in Annex I in 2001. With a market value at farmgate today estimated at more than US\$1 billion and representing close to 60% of the overall biocontrol market, microbials have gained strategic importance. This will continue in the future with the impressive involvement of the multinational plant protection companies, which focus on good technologies, and companies with the key strengths of uniqueness, product performance and effective barriers to entry while those without these strengths may be left on the sidelines. Consolidation will drive microbial biopesticide market growth through the increased market access and resources the large multinationals can bring. New Ag International asked Bill Dunham, Managing Partner of Dunham & Trimmer LLC in the USA and a co-editor of the 2B Monthly newsletter to investigate all ins and outs of this market.



BILL DUNHAM

BioControl has been the fastest growing segment of the global plant protection business (encompassing both non-crop and crop protection) over the last few years. And within biologicals, the microbial products have been the fastest growing product type segment of biocontrol today.

THE MOST IMPORTANT BUSINESS SEGMENT IN BIOCONTROL

Biocontrol is the most encompassing term for biological crop protection. It includes macro-organisms and all types of biopesticides.

Macro-Organisms are multicellular organisms that encompass insects, mites and nematodes. Because of their small size nematodes are often erroneously referred to as microbials. This is in error since they are multicellular organisms and are not single cell organisms.

BioPesticides is the term which covers BioChemical and Microbial products. Due to the need for an official registration, these products are easily identifiable. BioChemicals is a diverse group that includes plant extracts, plant growth regulators (PGRs), semiochemicals/pheromones and organic acids.

Microbials includes single cell microscopic organisms which consist of bacteria, fungi, viruses, protozoans and yeasts.

The Global biocontrol market is estimated at about 2.3 billion \$ (see graph 1). The largest subset of biocontrol consists of the microbial

products. There is a reason for this and is likely to be because of the higher hit rate in discovery screening, better production technology and quality control, as well as the ability to produce commercial products with a standard shelf life of two years, similar to traditional pesticides found in the global plant protection market. In fact the complete model of microbial discovery, regulatory, formulation and production is compatible to the entire new product discovery and development system of conventional chemical pesticides with many more similarities than plant extracts which require the production of a crop as the source of the active ingredient, or than semiochemicals that are very specialized and normally only effect one insect species and PGRs which again are very specialized.

One common error routinely occurs when discussing the value of the global biocontrol market. The value of the global biocontrol market has traditionally and continues to be discussed most of the time at the grower level, while the plant protection market comprising both the non-crop protection products and crop protection products is rarely presented at grower level, nearly always at manufacturer market value level. Many times this leads to a misleading comparison of the biocontrol



market values at grower level to the plant protection market values at the manufacturer level. This then suggests a much higher market share for biocontrol when comparing to the entire market of plant protection. The 2013 plant protection market at manufacturer level is normally reported to be in the range of \$55-\$60 billion US Dollars, while the 2013 biocontrol market value is normally reported at grower level in the range of \$2.2-2.4 Billion US Dollars. Biocontrol is reported as capturing 4% of the plant protection market, whereas it is more likely 3% when comparing like values.

**FIVE DIFFERENT
PRODUCT CATEGORIES**

Microbial pesticides (see Table 1) draw their name from naturally occurring microscopic organisms, or microbes, that are used to control pests. In some cases the pesticidal activity may derive from metabolites produced by these organisms. First the Bacteria: This includes a variety of unicellular organisms with insecticidal and fungicidal properties. The ability to manufacture these organisms through industrial fermentation, as well as an ability to store them for extended periods,

makes them ideal for use as biopesticides. This category is largely dominated by the *Bacillus Thuringiensis*, better known as Bt. Bts are bacteria that produce crystalline endotoxins, which disrupt digestive systems of many insect larvae. Bacteria account for about 75% of all microbial product sales.

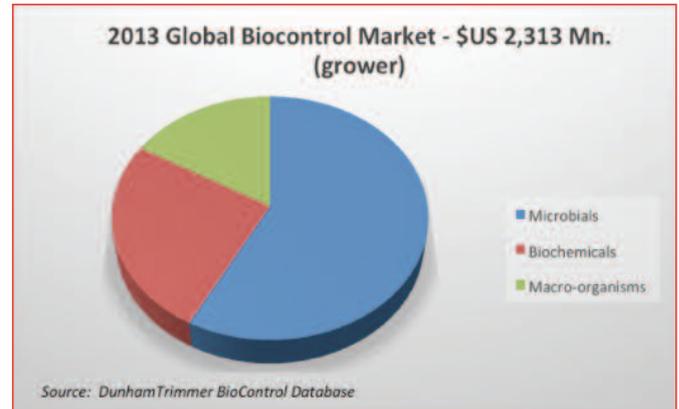
Then the Fungi: These fungi may display nematocidal, miticidal, insecticidal, fungicidal and/or herbicidal properties. They can also be manufactured through fermentation. In some countries, some fungi are also used as soil improvers and/or fertilizer substances: this is the case of *Rhizobium Japonicum* used for inoculating soybean crop to create symbiotic nitrogen fixation. This is also the case for *Glomus sp* used as additive to soil and substrates to establish endo-mycorrhizal symbiosis that in turn facilitates the root absorption of water and nutrients. Beneficial fungi account for about 10% of the market.

Viruses are the third most important subcategory. They are described as intracellular parasites. They are highly specific non-living organisms that consist of DNA or RNA material protected by a protein coat. When a virus comes in contact with a com-

patible host cell, the DNA or RNA material is injected into the cell's nucleus. Bioinsecticides derived from viruses include polyhedrosis viruses

interest translated in a number of R&D and commercial agreements but also in several acquisitions in this area. A partial list over the last 5

Graph 1: The global biocontrol market



and granulosis viruses, and can be used to infect plant-harming insects such as armyworms and bollworms. Viruses account for about 10% of the market for microbial products. Two other categories of products belong to the microbials: yeasts, which include a small group of products to control postharvest pathogens that promote fruit decay. These products may also act by stimulating natural defense mechanisms in crops; And finally Protozoa, which are single-celled organisms that can act as cellular parasites.

years of R&D/Commercial agreements appears in Table 2. In parallel, since the last semester of 2012, there have been more than two billion US dollars invested in acquisitions. The most important are listed in Table 3.

When looking at the recent acquisitions by the large multinational plant protection companies it quickly becomes obvious that they are more focused on microbial products than on macroorganisms and biochemicals. Macroorganisms require a specialized production using an insectary to produce the live predators or beneficials. Once produced expertise in maintaining live insects/mites/nematodes through a logistic system and delivery to the end user is needed. This normally leads to local production and multiple product sites. The pheromone business is again very specialized with a few companies dominating the actual produc-

Table 1: Types of Microbials

| Type | Target |
|----------|---|
| Bacteria | Fly and beetle larvae, caterpillars, fungal and bacterial diseases, Soilborne pathogens. |
| Fungi | Nematodes, whiteflies, aphids, thrips, beetles, locusts, grasshoppers, Fungal diseases, soilborne pathogens, weeds. |
| Protozoa | Grasshoppers, locusts, crickets. |
| Viruses | Caterpillars. |
| Yeast | Leaf spot, fruit drop, greasy spot |

**THE MAIN FOCUS OF THE
MULTINATIONAL CROP
PROTECTION COMPANIES**

The multinational agricultural input companies such as the crop protection multinationals have shown a strong interest in the biocontrol industry with the highest priority in the microbial market segment. This



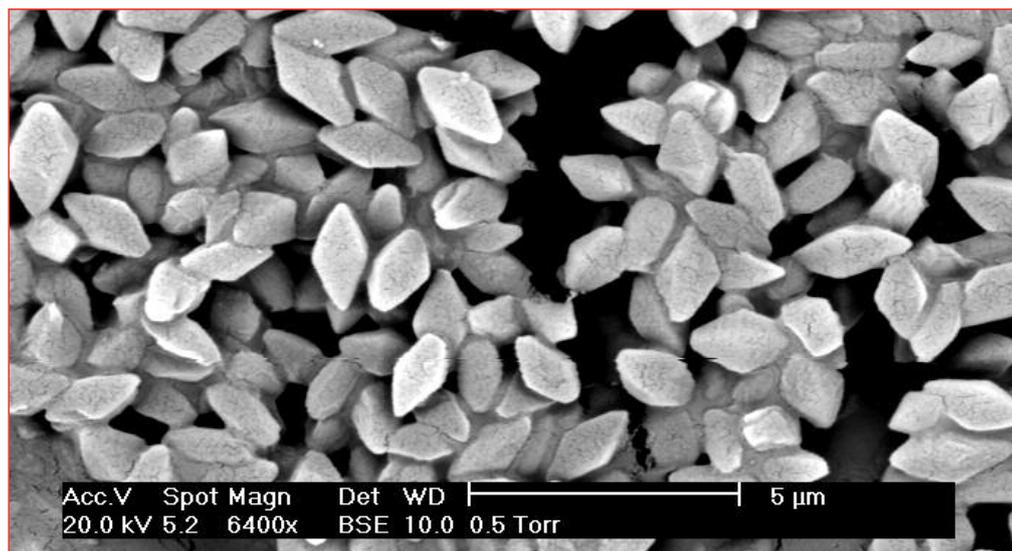


Table 2: Some recent (since 5 years) R&D/Commercial agreements

| Company A | Company(s) B |
|--|--|
| Arysta LifeScience | Plant Health Care |
| Certis USA | Summit Agro Mexico |
| De Sangosse | Biopreparaty / Servalesa |
| FMC | Cytozyme / Eden Research / Chr. Hansen |
| Gowan | Isagro |
| Koppert | Bayer |
| Marrone Bio Innovations | Valagro |
| Monsanto | Novozymes |
| Syngenta | Novozymes / Marrone Bio |
| Valent BioSciences | Biomar Microbials |
| OTHER AGREEMENTS: Amvac / Andermatt / Brandt / Bioworks / CBC Group / Koppert / Marrone Bio / MGK / Stockton | |

tion and development of new compounds as well as the specialized traps needed to optimize their field performance. Plant extracts depend on the consistent supply of the plant and a high quality assurance program in order to confirm that the active components of the extract are present year after year are at the required concentrations and proportions. This can be very demanding considering that the weather and stress the plant faces each year is dif-

ferent and has an effect on the chemical composition and levels of the active components. Microbial products on the other hand are normally produced either through solid fermentation (commonly fungal based products) or liquid fermentation (bacterial based products). Fermentation lends itself to the production strategy with which the large plant protection companies are familiar, that being large amounts of product at a single

Table 3: The most important acquisitions since 2012

| Acquiring Company | Company Acquired |
|--------------------|---------------------------------------|
| Bayer CropScience | AgraQuest & Prophyta |
| BASF | Becker Underwood |
| De Sangosse | Alpha Biopesticides |
| Koppert | Itaforte BioProdutos |
| Lesaffre Group | Agrauxine |
| Syngenta | Pasteuria & DevGen |
| Monsanto | Rosetta Green & Alnylam Pharma |
| Novozymes | Natural Industries & T J Technologies |
| Valent BioSciences | Pace International |

site. This is especially true when using liquid fermentation technology. Additionally, large production facilities for standard pesticide production employ computerized quality control processes to monitor production thus assuring consistency and the economics of scale. Fermentation technology easily lends itself to similar quality control methods in order to provide a consistent end product. This is especially true with bacterial based products such as Bt and other Bacillus products, which make up the largest portion of microbial biopesticides. Moreover, most bacterial based products can be formulated to have a standard shelf-life of 2 years, with no need for refrigeration in the logistics system. All of these characteristics of microbial biopesticides drives the natural interest of the multinational companies in microbial products, rather than biochemicals or macroorganisms.

ONE OUT OF 1,500 MICROBES INTERESTING FOR BIOCONTROL: ALMOST 100 TIMES MORE CHANCES TO LAUNCH A SUCCESSFUL COMMERCIAL PRODUCT THAN IN CONVENTIONAL PLANT PROTECTION!

There are several key drivers which are creating demand for biopesticides. (The term biopesticides is pur-

posely used here, because with the exception of Syngenta's (Originally Ciba-Giegy) investment in Syngenta Bioline back in 1992 all the inter-company agreements and acquisitions cover biopesticides.)

The four key drivers are Residues, Product Life Cycle Management, Regulatory Cost and the Timelines of New Product Development and last but not least Synergies from Combining Biological and Chemical Crop Protection:

Residues to start with: Food marketers and consumers are demanding reduced pesticide residues. Nearly all biopesticides have a food tolerance or MRL exemption based on their low toxicity and safety profiles.

The second main driver is the Product Life Cycle Management: Companies have invested huge sums developing and commercializing existing conventional products in their portfolios. Effective pest resistance management strategies are critical to protecting this investment to extend the life cycle of these products. Biopesticides, which have a more complex mode of action, makes them valuable resistance management tools.

The third driver is the Regulatory Cost and the Timelines of New Product Development (see Graph 2): For new conventional plant protection products, CropLife America documents that to discover one successful commercial chemical active ingredient as many as 139,000 candidate chemical compounds must be synthesized and screened. The successful registration of such a product today averages close to 10 years from the time of discovery and includes many long term toxicology, environmental fate, and crop residue requirements. The complete cost of launching a new conventional chemical active is in the range of \$150-\$265 million US dollars, based on CropLife industry surveys.

A big difference with new microbial biopesticide products! Biological industry leaders estimate that one out of every 1,500 to 2,000 microbes screened results in a suc-

successful find. Registration timelines are shorter as well, especially with US-EPA and Canada-PMRA. Expensive long term toxicology, environmental fate and crop residues data are rarely required since the microbial or plant based extracts are already commonly found in the environment or in plants that have been consumed by humans for decades or centuries.

This reduced cost of investment to develop a new microbial biopesticide is quite important when Return On Investment (ROI) is considered and compared to that of synthetic pesticides. Large crop protection and financial companies commonly use Discounted Cash Flow (DCF) models to evaluate investments in new products and technologies. DCF takes into account the value of money over time to calculate the Net Present Value (NPV) of an investment. The challenge for conventional pesticides is not only the much higher registration cost, but also the long period (minimum of 10 years) of investment prior to any sales. For microbial biopesticides the upfront cost of development is much lower and the development timelines are much shorter. This provides a much more positive NPV, even if the projected sales are lower than with a synthetic pesticide.

Last but not least, there are synergies from combining biological and chemical crop protection: The majority of biopesticide companies are based on one or two technologies, while distributors and growers seek complete crop protection solutions. Due to this limitation, most biopesticide companies are small and lack market access due to restricted available resources (both money and manpower). On the contrary, Global Plant Protection Companies have extensive sales and marketing organizations (market access) for immediate global market growth. They offer the opportunity to combine biopesticide technologies with existing portfolio to offer complete solutions to growers and distributors. They can provide much greater resources to support biopesticide

product R&D, registration, manufacturing, and marketing. The base strategy of the main plant protection companies is that of offering a complete portfolio of products to the growers in order to become the grower's source of all plant protection products, rather than trying to compete on a product by product basis.

A COMMON DRIVER TO THE MOST RECENT ACQUISITIONS?

Beyond the common strategy of the main plant protection companies to offer a complete portfolio of prod-



ucts, Dunham Trimmer (DT) has analyzed the most recent acquisitions by the multinational plant protection companies. The key facts used in the analysis are based on publicly available information released on each transaction and is not based on any confidential information that may have been obtained or shared by anyone associated with the purchase. This analysis strictly represents DT assessment based on the company's knowledge of the market and assessment of how each party may have approached the agreement. (See separate box)



Is there a common driver to all these deals? Maybe not as appears in the analysis of the various deals but there are common consequences!

The most important aspect of these and subsequent mergers of the conventional pesticide companies and



biopesticide companies will be increased market access for the biopesticides and especially microbial products, through availability and utility of greater resources, which will lead to faster commercialization and a broader, global market presence. Additionally, they will bring an increased credibility for microbial biological solutions, increased biopesticide R&D investment as well as capabilities and resources to substantially increase the use of biopesticides. As a result more products will be brought through the development cycle at much greater speed and allow more combinations of biological and conventional chemical approaches for the grower. Major companies will look to combine technologies to benefit both biopesticides and traditional pesticides, offering growers whole crop solutions. These and future mergers / acquisitions address

consumer demands for lower pesticide residues, particularly in fresh produce. Some independent biopesticide companies will struggle to compete and find the right partner, especially those lacking key factors for investor attractiveness and those companies with only a single technology. Not all conventional chemical companies will succeed in the transition to biopesticides either. They will need to learn how to evaluate, develop, and market biologicals differently from their traditional products, training field staff, learn new manufacturing and logistics to meet the differences for biologicals which many times are more demanding.

MORE CONSOLIDATION AWAITED

The Market Drivers for microbials and biological products are sustainable and provide tools for managing pesticide residues in crops, include substantially lower cost to develop, and shorter registration timelines in US & many other countries. Biopesticides can also be used with conventional chemistry as product life cycle management tools with complex mode of action for managing pest resistance by combining biopesticides with conventional crop protection chemicals in integrated pest management programs, enhancing the benefits of both product lines. Biopesticides are very useful in fresh produce for the Export Markets/Supermarkets/Consumer Demand for managing chemical residues.

It is therefore logical to expect these consolidation trends and interest in biopesticides, especially microbial products, to continue by the multinational plant protection companies with focus on good technologies and companies with the key strengths of uniqueness, product performance and effective barriers to entry while those without these strengths may be left on sidelines. Consolidation should drive microbial biopesticide market growth through the increased market access and resources the large multinationals can bring. ■

An Analysis of six recent deals in the Biocontrol industry

Bayer – AgraQuest (Announced - July 2012 / Closed – August 2012)

Key Facts:

- First major biopesticide acquisition by global crop protection company
- Bayer acquired all existing products, product pipeline, and manufacturing facilities
- AgraQuest commercial products included Serenade, Ballad, Requiem, Sonata, and others
- AgraQuest sales estimated at time of acquisition was approximately \$40 million US dollars
- Purchase price \$425 million plus milestone payments

Analysis:

- Believe this was a strategic decision after significant study of the market by Bayer CropScience to enter the biopesticide market based on an analysis of the option of organic growth or large purchase
- Bayer previously acquired selected biological technologies and assets of AgroGreen, including the products BioNem and Shemer, in 2009 and 2010
- AgraQuest provided Bayer with an experienced team combined with products, pipeline, and manufacturing capability and immediate market presence as opposed to delayed entry while building internal capability & obtaining registrations (organic growth)
- We believe Bayer's analysis concluded the opportunity cost considering time and investment of building an internal capability was higher than purchase price for AgraQuest based on a NPV calculation
- Bayer resources and market access should allow it to rapidly expand sales of AgraQuest products
- Bayer subsequently purchased Prophyta in January 2013 to expand its biological offer and manufacturing capability
- Contans is Prophyta's main product which is used for control of Sclerotinia diseases
- Prophyta also brought additional manufacturing plant with very knowledgeable and extensive expertise in solid state fermentation

BASF – Becker Underwood (Announced - September 2012/Closed – November 2012)

Key Facts:

- Largest individual acquisition of a company with biopesticide products by a global crop protection company
- BASF acquired existing products, product pipeline, and manufacturing facilities
- Becker Underwood was a leader in seed coatings (polymers and colorants) and biological seed treatment
- Becker Underwood sales forecast was estimated to be at \$250 million in FY2012
- Purchase price \$1.02 billion
- BASF formed new business unit, Functional Crop Care, in January 2013

Analysis:

- Believe the focus of this acquisition for BASF was seed treatment capabilities, not primarily biocontrol
- BASF sought greater strength in the seed treatment R&D and commercialization to utilize with both conventional and biological actives
- Becker Underwood seed coating expertise provides BASF with key capability in developing new seed treatment products
- The acquisition was based on existing actives or new offers including biologicals
- "BioStacked" seed treatment solutions like VAULT HP were added benefit, and certainly desirable, but may have not been driving decision for acquisition

Syngenta – Pasteuria Bioscience

(Announced - September 2012/Closed – November 2012)

Key Facts:

- Targeted acquisition directed at nematode control, not necessarily biocontrol
- Syngenta previously had executed a development agreement with Pasteuria to evaluate the seed treatment technology for soybean cyst nematode control in June 2011
- Syngenta acquired novel biological nematicide technology with a unique mode of action and proprietary in-vitro production process
- Pasteuria sales were not publicly disclosed
- Purchase price \$86 million with deferred payments of up to \$27 million

Analysis:

- Believe the focus of the acquisition for Syngenta was an effective low toxicity nematicide
- Pasteuria offered a novel nematicide with proven performance and strong IP in use and production
- Syngenta obtained hands on experience with the Pasteuria product through their prior development agreement
- Unclear if Syngenta's strategy was to obtain a biological solution or just a low toxicity nematicide
- Syngenta market access exponentially increases Pasteuria product potential
- A very rapid launch of Clariva seed treatment in soybeans based on Pasteuria technology has already been initiated

FMC – Chr. Hansen – CAEB (Announced - October 2013)

Key Facts:

- Three way deal including acquisition of Center for Agricultural & Environmental Biosolutions (CAEB) by FMC combined with expanded cooperation agreement between FMC and Chr. Hansen
- Builds on the existing relationship between FMC and Chr. Hansen which resulted in launch of new biological product, Nemix C, in the Brazilian sugarcane market
- Establishes CAEB facility in RTP, NC as biological R&D center for FMC globally
- Financial terms of CAEB acquisition were not disclosed

Analysis:

- Believe FMC was seeking to establish biological discovery and development capability
- Chr. Hansen provides fermentation development and manufacturing scale up expertise
- CAEB brings microbial library, intellectual property, and discovery capabilities
- FMC provides development and registration expertise together with global market access
- Overall objective to develop a platform to discovery, develop, register, and commercialize biological solutions on a global basis
- Gives FMC a discovery capability to produce proprietary product candidates for FMC commercial organization
- Provides alternative source of new technology in addition to licensing

Monsanto – Novozymes (Announced - December 2013/Closed – February 2014)

Key Facts:

- Forms a long term strategic alliance called BioAg Alliance
- Combines Novozymes expertise in microbial discovery, development and production with Monsanto capabilities in advanced biology, field testing, registration and commercialization
- The two companies will maintain separate and independent microbial discovery efforts
- Monsanto will be responsible for marketing all microbial biologicals, including the current Novozymes portfolio
- The companies will co-fund and co-manage the biological R&D efforts
- Monsanto paid Novozymes \$300 million in upfront fees in recognition of Novozymes ongoing business and microbial capabilities

Analysis:

- Believe Novozymes sought to improve capabilities in field testing, registration, advanced biology, and market access
- In addition, Monsanto enhances biological discovery through access to Novozymes expertise in microbial discovery, evaluation, production processes and scale-up
- Transition to Monsanto handling marketing for existing Novozymes products in 2014, gives the BioAg Alliance immediate commercial products, and gives Novozymes products much broader market access
- The partnership should increase the number of strains being screened, identify better candidates, and bring them to market more quickly than either company could on its own
- BioAg Alliance has capabilities to provide grower solutions utilizing genetic traits, seed treatment, traditional agricultural chemicals, biologicals, and precision ag
- Subsequent to BioAg Alliance formation, Novozymes announced plans to establish a \$36 million R&D center dedicated to bioagriculture in RTP, NC

Marrone Bio Innovations – Valagro (Announced - May 2014)

Key Facts:

(though not an acquisition this is one of the first formal agreements between a biopesticide company and a biostimulant company focused mainly on microbial development)

- Collaborative discovery and development agreement
- The companies will provide each other access to IP, active ingredients, end use formulations and cooperate on performance evaluation of combinations of technologies for commercial use
- Valagro will evaluate its biostimulants in combination with MBI biologicals
- MBI will evaluate Valagro biologicals for pesticidal activity
- Both companies will cooperate in developing MBI biostimulant leads using Valagro expertise
- Further details not available as agreement just announced

This analysis is provided by DunhamTrimmer Consultants for New Ag International