Chapter 16

Development of Biopesticides and Future Opportunities

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Abstract

Biopesticides, pesticides based on living organisms or their extracts, are increasing in sales around the world, as synthetic pesticides are less available and environmental and health issues drive new approaches. Despite the increasing sales and use, there are still limitations that restrict more widespread uptake, such as slow to kill, cost, difficulties of production, lack of appropriate formulations, and reputation based on previous poor performance of biopesticides. Regulation continues to be problematic in many countries, as the processes are designed for evaluating chemistry rather than live organisms. Biopesticides do have a bright future, given the amount of investment currently in the area, improving products and growing need.

Key words Entomopathogens, Biopesticides, Regulation, Product development

1 Introduction

A number of recent reviews (e.g., [1–4]) have outlined the bright predictions for biopesticides sales in the coming years. Independent assessments have suggested increases of up to 15% per annum worldwide, although any such figures are hard to verify. But these reports do indicate biopesticides may be entering a new era of mainstream use, rather than niche market products. This book has provided chapters addressing some of the technical requirements of biopesticide development, such as production, formulation, bioassay, and application. However, the process of getting products into markets is based on far more than just technical development. The commercialization process for taking effective microbial agents through to available biopesticides has many legislative and marketing issues, as well as some technical limits common to many potential products.

1.1 The Need

There is no doubt the need for new pest, weed, and disease control products is growing. Pests have been estimated to cause between 27 and 42% losses in production for major crops around the world. This would rise to an estimated 48–83% without crop protection

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products, such as synthetic chemicals [5, 6]. The green revolution, the massive increase in food production in the past 50 years, is partly based on great increases in the use of synthetic pesticides (15–20 times) [5, 6]. It is likely that changes to climate patterns will exacerbate crop damage by pests and disease. The need for pesticides is increasing at a time when new synthetic agent leads are decreasing [2]. There is also pressure on current control approaches in terms of environmental and mammalian safety, with many countries moving to banning outright some groups of chemicals used in pesticides [1, 7].

1.2 Increasing Use of Microbial-Based Biopesticides

There are an increasing range of biopesticides being registered around the wrold (Table 1). It has been noticeable in the last 5 years that the major pesticide companies around the world have been acquiring small- to medium-sized biopesticides companies and/or products [8]. The acquisition of Agraquest and Prophyta by Bayer CropScience, Becker Underwood by BASF, Pace International by Valent BioSciences, and Pasteuria BioScience by Syngenta [8] shows the value of the growing market. At least one of these purchases was for over $1B US, although the company bought had more than just biopesticides as existing products. This reflects both the growing need for novel products as pesticides are withdrawn, and the recognition that the market is ready for these products. This has led to changes in the type of biopesticides that are likely to be successful. The largest pesticides companies are working in the largest agricultural and forestry markets, therefore most interest is shown in biopesticides with application for high value crops, such as horticultural crops with pests and disease including thrips, whitefly, powdery mildew, and *Botrytis.* This differs from the history of microbial-based biopesticides, which were more often niche, regionally developed products often targeting single pest species on minor crops.

Reasons for increasing use by growers and farmers include the following benefits:

- Efficacy against the target pest. Strain selection and new formulation and application techniques have increased the efficacy of many microbial-based products.
- Production efficacy. The yield and quality of the active agents has been improved in many cases.
- Host specificity. Host biological agents are more limited in host range than synthetic pesticides, which have made them more attractive for both environmental safety and registration viewpoints.
- Can be used in Integrated Pest Management (IPM) programs.

- Useful for resistance management. Resistance development to agents with an infective action (as opposed to those reliant on a toxin) has rarely been found following years of field application.
- Useful for residue management. In most cases, biological agents are not considered residues on produce.
- Growers—crop management, many biological agents have no worker reentry interval so growers can harvest when it is best for the crop.
- Worker safety. Microbial agents are screened for mammalian toxicity and not used if there are any issues.
- Favorable environmental footprint. In an era of concern over environmental pollution of all types, the biological and biodegradable nature of microbial-based pesticides is highly favorable.
- Use in organic production. Depending on the formulation ingredients biopesticides are suitable for use in certified organic production.

2 Regulation

Most countries have a regulatory process for pesticides. As has been well covered elsewhere [1, 7, 9, 10], many of these regulatory processes have not been updated for specific needs of microbial-based biopesticides, meaning some of the requirements are not fit for purpose.

Regulation is needed for any pesticide. Reasons include:

- Protection of the natural environment
- Protection of human safety
- Maintain consumer standards
- Protect farmers and growers by having quality standards

Table 1
Examples of products from the USA

	Bioinsecticide	Biofungicide	Bioherbicide	Bionematicide	Other
Microorganism Bt[a]	44	–	–	–	–
Microorganism non-Bt	18	41	5	3	1
Botanical	8	6	1	2	29
Semiochemical	56	–	–	–	–
Other	25	8	3	0	29
Total	151	55	9	5	59

[a] *Bt Bacillus thuringiensis*

- Protection of technological invention
- Protection of rights
- Maintain product standards

The issues of harmonization of regulations across the world continue to plague biopesticide development. Most jurisdictions have not developed specific guidelines for assessment of biopesticides based on live organisms, resulting in inappropriate registration procedures largely derived from assessing synthetic chemical-based pesticides. Some countries have developed specific guidelines, such as the USA Environmental Protection Agency (EPA).

Another complicating factor is that it can be difficult to import products based on live organisms into new regions, due to concerns around exotic organism introductions.

2.1 Data Requirements for Registration

For registration of biopesticides, each jurisdiction has requirements for the data package submitted. The EU and EPA requirements, for example, do currently differ, but have enough similarities that it is possible to generalize.

Data requirements for an active substance usually include:

1. Identity and purity
2. Physical and chemical or biological properties
3. Further information on use, production processes, and related areas
4. Analytical methods used to identify the active(s)
5. Human health effects
6. Residues (often confused with persistence)
7. Fate and behavior in the environment
8. Effects on nontargets
9. Summary of all

Data requirements for the formulated product:

1. Identity and composition of the formulation
2. Physical and chemical properties
3. Application, labeling, and packaging
4. Further information
5. Analytical methods
6. Efficacy data
7. Toxicology and exposure
8. Residues
9. Fate and behavior in the environment
10. Effects on nontarget organisms
11. Summary

The data on these requirements is compiled into a "dossier." Components of the dossier are used in risk assessment; hazard or exposure information about the active substance and/or product. It is generally required or at least good practice to have studies conducted in laboratories of GLP standard. The dossier will contain data from studies and trials, published papers which contain findings relevant to answering the regulatory question—either single papers or the 'weight of evidence,' specific pieces of information (e.g., "The product will be applied to cereals") and waivers, also known as scientific justifications, where it is explained that the data requirement is not relevant because of a specific reason—this use of waivers is essential for biopesticides.

3 Areas of Potential Improvement in Biopesticides

What would make biopesticides more effective or increase market share of effective biopesticides? Some of the identified limitations that have reduced biopesticide uptake include:

- Lack of highly virulent strains.
- Slow to kill.
- Environmental constraints.
- Lack of suitable stage for mass production or application.
- Complex life cycles of agents.
- Complex handling requirements.
- Variable effects, due to any combination of the above.
- Expensive in comparison to synthetic pesticides.
- High production and research costs.
- Lack of profits for companies.
- Regulatory constraints.
- Problems with formulations and marketing.
- Expectations are often of a chemical equivalent: fast acting, cheap, and broad spectrum.

3.1 Improving Regulation

As stated earlier, biopesticides are required to be registered in most markets. The regulations often used the same system as for chemical pesticides. In some cases, such as the EU, registration is a two-stage process, with both the active substance and the product registered separately. It can take 4–5 years to achieve registration and the cost of the full dataset for registration can be significant (over € 500M), although this is still cheaper than registration of synthetic chemical pesticides in most cases. There is a move around the world to harmonize biopesticide regulations but this is still in development in most countries.

Reflecting the farmers and growers interest in using biopesticides and the increased demand for these types of products, the FAO, a global organization, are updating and expanding their guidance for microorganisms, botanical and semiochemical-based pesticides and use of these technologies.

This new guidance document considers pest control agents based on microorganisms, botanicals, and semiochemicals. These are distinguished from conventional chemical pesticides by a combination of their active substance material and/or nature. The view that biopesticides have characteristics that require particular consideration for registration is shared by USA-EPA, the EU, and the OECD Biopesticide Steering Committee and many countries are involved in this work, developing a harmonized approach to 'biopesticide' registration (USA, Canada, EU, Japan, Australia, New Zealand). In acknowledgment that biopesticides are a special situation, specific biopesticides registration guidelines have also been developed by certain countries (Brazil, China, Ghana, Kenya, and Southeast Asia). However, in many countries, microorganisms, botanicals, and semiochemicals are evaluated and registered following the same system as for conventional chemical pesticides; this approach can pose an unnecessarily high regulatory burden to satisfy inappropriate testing requirements.

Harmonization of data requirements and of procedures for registration was recognized as an important step to facilitate the availability of microorganisms, botanicals, and semiochemicals. The guideline describes the basic data requirements and evaluation for field trial permit and registration for these technologies. This updated guidance will be available in 2016.

3.2 Strain Selection

There are a number of areas where advances may result in better biopesticide uptake. As detailed in some of the methods in this book, bioassay is a standard and necessary approach to biopesticide development. However, laboratory bioassay results do not always translate to field success, given the complexity of ecosystems and climatic effects. But efficient bioassay can be the crucial step in separating potentially useful strains from the vast array of microbial candidates.

Many researchers are now looking for methods to more rapidly identify the most appropriate strain of a microbial for use in biopesticides. Less than 1 % of candidate isolates eventually make successful products, so methods that can improve the search approach are sought. Recent approaches have included use of massive DNA sequencing to directly target activity-related genes, rather than testing each microbe. The success of such approaches is still to be seen.

3.3 Production and Formulation

Production remains one of the key areas for making biopesticides cost effective. Microbial agents are often very effective when applied at high rates, but the cost of production precludes their use. In this book, several production protocols are outlined.

Further improvements and efficiencies gained in production will continue to make biopesticides more successful.

Formulation has provided some of the more effective improvements in the biopesticides area in the last decades. The use of prills and emulsions, techniques covered in this book, continues to improve the application, persistence and efficacy of biopesticides. Seed coating, also covered herein, is a new and increasingly attractive method to deliver biopesticides, especially in the soil. Seed coating is increasingly attractive as more agents are shown to be rhizosphere colonizers or even capable of endophytic colonization.

3.4 Application and Monitoring

Following production and formulation, the microbes and their bioactives need to be delivered to the target pest. This is one of the most challenging steps in the use of biopesticides, partly because most application techniques were originally developed for synthetic pesticides, not live organisms. Ideally application establishes the active agents in contact with the pest and/or maintains activity for several weeks. Spray applicators have routinely been used for aboveground application. There is increasing focus on the basics of spray application with microbial agents, including specialized equipment, optimal droplet size, and targeted application. Application subsurface is more problematic, as delivery is difficult without damaging the soils and plants. However, once delivered subsurface, persistence is often higher than aboveground applications.

3.5 Quality Control

Product variability has been a major issue in biopesticide development, but quality control to standardized batches is now generally recognized and incorporated into production systems. Ideally, each production batch is tested for efficacy against a target insect, stability, and propagules (yield).

3.6 Environmental and Mammalian Safety

One of the driving forces behind the increasing sales of biopesticides has been market pull. Biological agents are perceived as more inherently safe than synthetic chemical pesticides. However, all products and agents still must pass rigorous safety testing for most regulatory regimes. This book provides some methods around safety evaluations. It is likely to become more of a focus as more is understood about the mode of action of biological agents, the increase in use of bioactive directly rather than whole organisms, and as part of the wider public perception and concerns over risks.

4 Innovative Approaches

While incremental improvements are constantly made across all areas of delivering effective biopesticides based on microbial agents, there are several approaches which offer new paradigms for using microbial agents. Aspects of these are covered in this book.

4.1 Endophytes

One of the rapidly growing areas of investigation is the exploitation of plant endophytes. Fungi and bacteria are commonly found within plants and can confer significant pest and disease resistance [11]. In New Zealand, the pastoral industry almost exclusively used grass with *Epichloë* spp. endophytes, which confer pest, disease, and drought tolerance [2].

Many microorganisms used in biopesticides also deliver a number of additional benefits beyond virulence to a primary target. For example *Trichoderma* spp. can enhance the uptake of soil macro- and micronutrients by plants and substantial plant growth benefits in the absence of a disease. Entomopathogenic fungi can also have antagonistic activity against plant pathogens attacking the same crop. Endophytes are all about chemistry. They produce a range of bioactive secondary metabolites (such as alkaloids). The type of alkaloids produced depends on the strain of fungus present. The host plant has a major effect on the quantity of alkaloids. The chemistry of endophytes is diverse and complex.

The literature on endophytes is growing exponentially currently, suggesting new products or plant varieties are likely to emerge.

4.2 Bioactives

The use of just the active component of biocontrol microbial agents has long been attractive. The most successful microbial control agent in used commercial products, *Bacillus thuringiensis*, kills insects through toxic proteins, rather than an infective action. Serenade, a products based on *Bacillus subtilis*, contains live microorganisms and a combination of known and novel lipopeptides (agrastatins). In these cases, it may not always be necessary that the microbe is alive for a product to be effective, as the bioactive effect is present due to secondary compounds. Microbial secondary compounds can be produced and optimized in fermentation, which can make the process very amendable to scale-up and optimization. Microbial secondary compounds can also have more of a synthetic pesticide equivalence, making them easier to incorporate in current pest management practice. Depending on the nature of the secondary compounds, there may need to be consideration of residues on food and potential of resistance development in the targets.

5 Integrated Pest Management (IPM)

Biopesticides fit IPM systems well, usually being compatible with other biologically based controls (e.g., parasitoids/predators). Integrated pest management is not a new idea, but its application is dependent on having a range of tools that can be combined to reduce pest impacts below economic thresholds. These tools can include environmental safe chemicals, semiochemicals, plant varieties, physical methods, decision support tools including monitoring and biopesticides. The main ingredient of IPM is that the activities and tools act together to lead to pest management. The European Union has enacted legislation designed to strongly encourage the use of IPM [1].

Several companies are actively promoting the combined use of biopesticide and synthetic pesticide, such as the company Bayer with Votivo, based on *Bacillus firmus* for nematode control, combined with a synthetic insecticide, Poncho, as a seed treatment.

6 Summary and Future Directions

As demonstrated by the increasing sales, acquisition of small production companies by large companies, and the new products entering the market, the future for biopesticides looks very promising. Largely driven by market need, with many current synthetic chemical pesticides used in control being withdrawn, biopesticides have become the main pesticides used in some sectors in some regions. However, as detailed in Glare et al. [2], there are specific areas where research can lead to step change in the uptake of biopesticides. The review recommended:

- More research emphasis on delivery and persistence of biopesticides in the field. The aspirational target for persistence on foliage was put at 21 days and, in soil, persistence at the site of pest occurrence, rather than just persistence.
- More research emphasis on the chemistry of bioactives from microorganisms. This was seen as an area underdeveloped.
- More strategic selection of target pests and markets. The economics of biopesticide use can still be constraining so targeting of high value markets and highly susceptible pests is necessary.
- Continued investment in expertise for the discovery, development, and implementation of biopesticides. Biopesticides remain an underresearched area and additional investment in research from fundamental to applied subjects will reap benefits.
- Registration and legislative changes to better align data requirements with the features of biopesticides.

Similarly, there are features of successful biopesticide development that are common. Some of these are as follows:

- Take-up of biocontrol agents often depends on commitment and drive of scientist involved. It is surprising how important a product champion can be to the success of microbial biopesticide development, especially in the prototype stage.
- Well-defined end user demand and market position.
- Products developed in partnerships with commercial producers. Prototype products are often developed by researchers in

public institutions, with a lack of commercial knowledge or developed pathways to market. The combination of commercial acumen and research capability is crucial.

- Market demand for products. This includes realistic assessment of competing products and costs.
- Policy framework encourages uptake. As discussed herein, regulation designed specifically to consider biopesticides can be an advantage and cost savings.
- A pragmatic approach by goverments to regulations and registration.
- Government funds work and/or subsidizes product. Development of biopesticides from the many possible agents is expensive and can fail. Public investment in research leads to more products being developed.
- Support from researcher/first developers. It has been demonstrated many times that involvement of researchers after the first stages of commercialization improves the success rate.
- Good quality control of final product. The quality of products that reach the user is more of an issue for those based on live organisms than other forms of pesticides.

Progress has clearly been made. There are many new products coming on to the market. Technological developments are continuing to overcome impediments. However, biopesticides have not yet reached their potential, even though all predictions suggest biopesticides will outperform other pest control options in terms of market share increases in the near future.

We see a bright future for biopesticides, if the research and industry groups can think bigger and act united, better communicate the positive messages about biopesticides, and demonstrate their ability to control pests effectively and economically.

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