



The Fascinating Journey from Discovery to Product

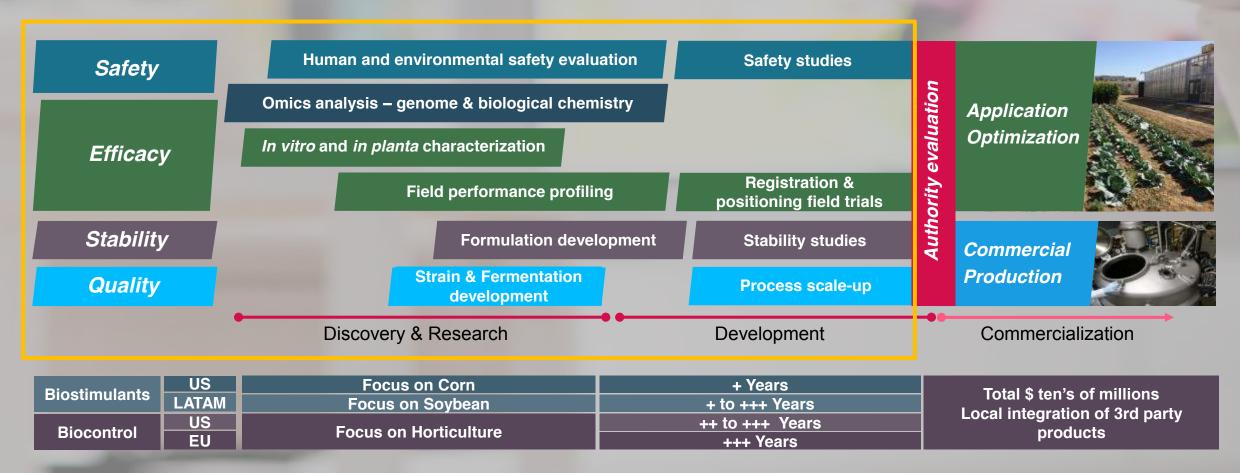
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From idea to market, there are many steps to get to a consistently performing Biological product



Development from discovery to market is complex but with approximately one tenth of costs and 5-8 years faster in the market than chemical pesticides

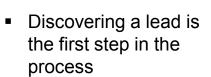


So what's involved?

Discovery and Research









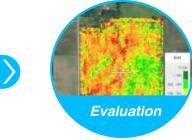
Identification / confirmation of mode of action

Testing in predictive assays



Strain Optimization and Process Improvement





Broad greenhouse and Worldwide Field Testing



Discovery and Research followed by Development





Discovery

- Bioinformatics
- # Metagenomics
- # Microbial genetics
- Metabolomics and Proteomics



Understanding Biology

- Plant microbe interaction
- Mode of action of biologicals
- # Microbiome
- Early field characterization
- # Safety



Fermentation & Formulation

- # High throughput fermentation
- # Production (submerged and solid state)
- # Shelf life & stability
- Compatibility



Field Testing

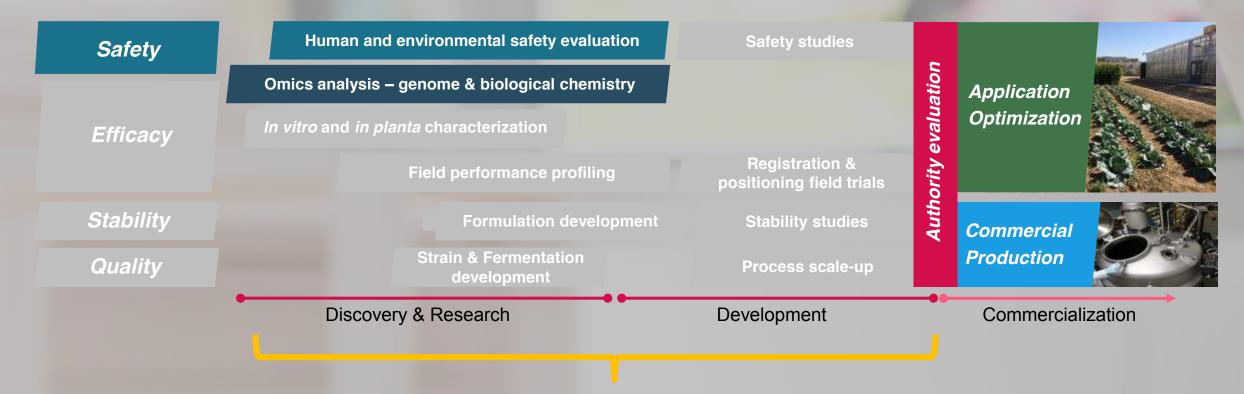
- Registration trials
- # Positioning trials



Moving towards Commercial

- # Regulatory
- # IP / Freedom to operate
- # Supply chain
- # Commercial

Safety in the Research Phase



Intellection Property - Protecting your investment



Safety during Research phase

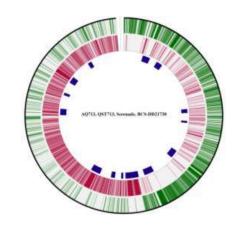
Before we spend money on trials, can we get genomic information that will help?

Before we go to field or scale up a fermentation process...

Non-GLP mouse oral tox?

Some countries require bee testing before any field trials

Have we determined Plant Safety (phytotoxicity)?

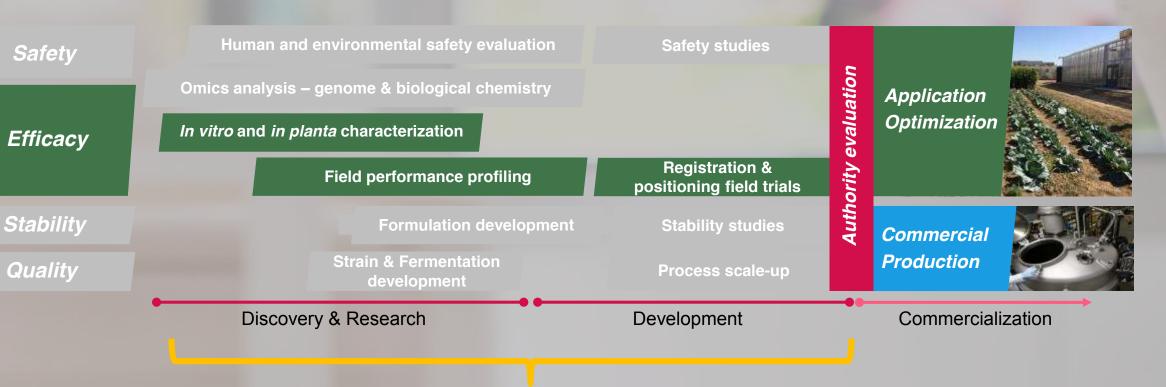






Let's focus on Efficacy...

Safety



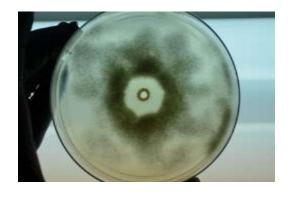
Intellection Property – Protecting your investment



Characterizing Efficacy

Making the jump from lab to field can be a big hurdle

Primary in vitro screening





Screening on plants





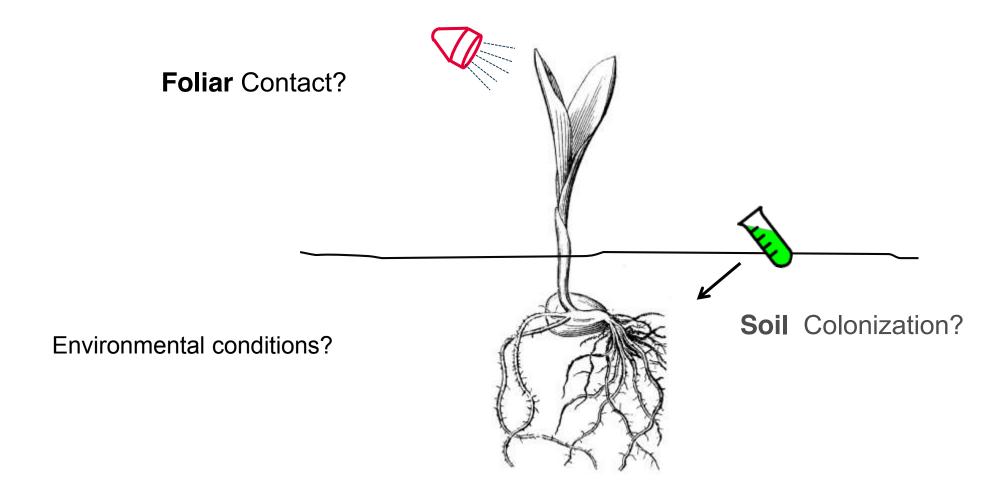
Field Trials on final target





Understanding mode of action aids in field transfer

What conditions will give your discovery the best chance of success?





Efficacy during Research

Proof of Concept – moving to the field

QUESTIONS TO ADDRESS:

- Best crop and target based on research results
- Efficacious dose
- Spray intervals needed
- Can adjuvants help?
- What are the right controls?

Field trials, what's important

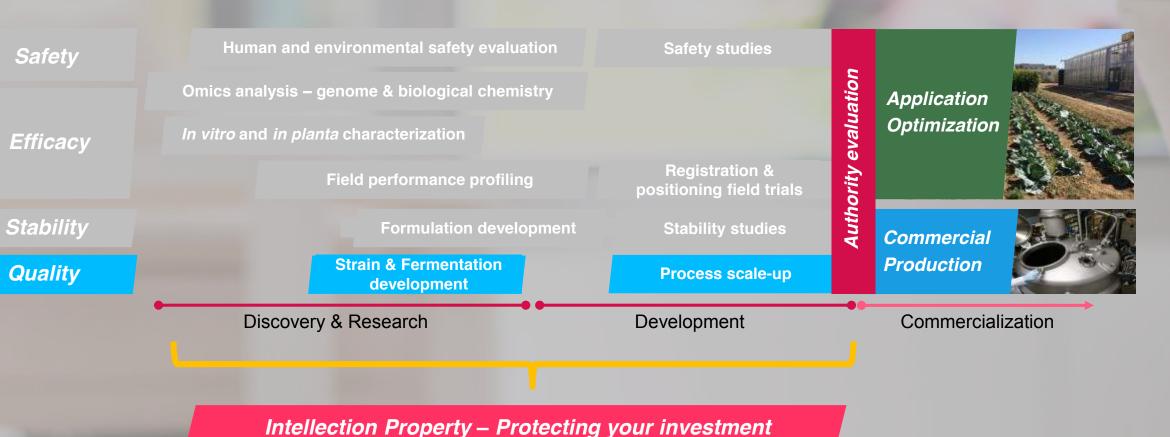
Proof of concept, stand alone, programs

Regulatory trial





Quality and profitability or cost of goods (COGs)



Safety

Quality



Biological Process Development

Integrated Approach to Developing a Microbial Fermentation Process

Goal:

To develop **cost-effective**, robust process for commercial production of microbial active ingredients

Integrated Approaches:

Fermentation - Physiology, differentiation, biosynthesis - Growth media (C, N ...) - Growth conditions (pH, temp, DO) Yield ↑ Cost ↓ Fermentation Strain Improvement - Eliminate genetic bottlenecks - Reproducibility - Scalability







Small







Biomass

- cell density
- morphology
- sporulation
- CFU

Biological chemistry

- analytical
- metabolomics

Bioactivities

- in vitro
- in planta

Physi/chem properties

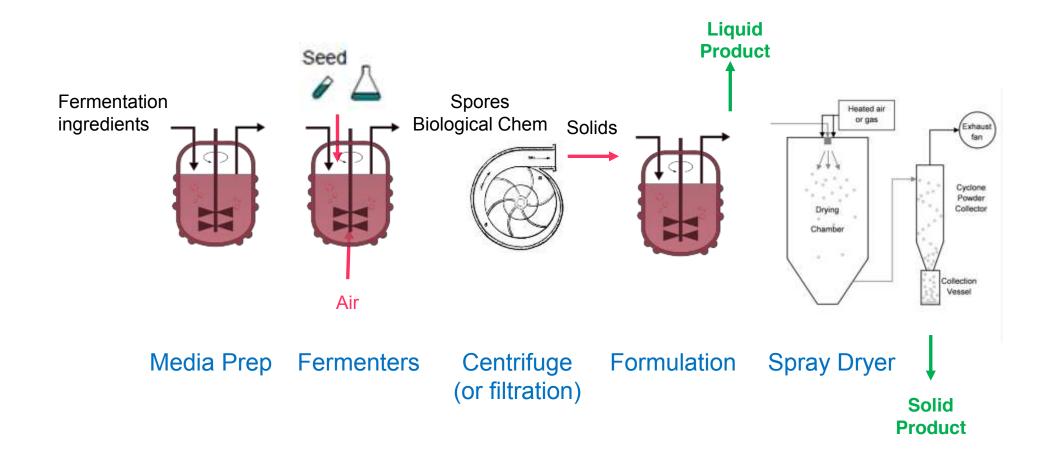
- pH
- viscosity
- solids

→ Pilot plant 300 - 3000L

3-30x



Process Flow Diagram





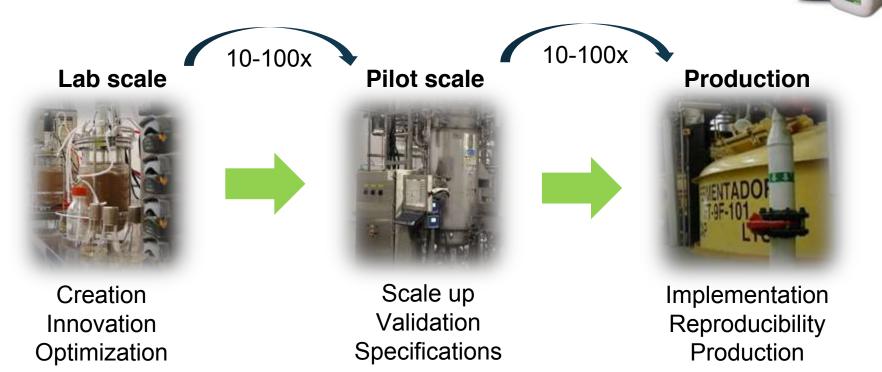
Scaling up the process during Development

The Critical Link between Research and Manufacturing



Convert microbial discoveries into commercial products

Manufacturing process: fermentation & formulation





Process Development



Transforming microbial discoveries into commercial products



Create manufacturing process & formulation



Active Ingredients





Concentration/stabilization





Final product



How to interest a partner in development and commercialization





Preparing for Registration

Development Phase

US EPA BIOPESTICIDE Data Requirements

FIRST REGULATORY AGENCY TO DEVELOP SEPARATE DATA REQUIREMENTS AND STUDY GUIDELINES

- •MICROBIAL
- BIOCHEMICAL

SEPARATE DIVISION WITHIN EPA TO REVIEW BIOPESTICIDES

- BUILDS KNOWLEDGE AND EXPERTISE
- TWO DIVISIONS
 - MICROBIAL
 - BIOCHEMICAL

REVISED DATA REQUIREMENTS ISSUED IN 2007 TO FURTHER CLARIFY THE REQUIRMENTS.



History of Biologics Safety Assessment: US EPA

- 1948 First microbial pesticides registered in the US
- 1974 EPA sponsors workshops, symposia and panel discussions to identify relevant safety concerns for microbial pesticides
- 1979 EPA commissions expert panel "Human Hazard Evaluation Scheme for Biorational Pesticides" – becomes basis for future regulation
- 1983 EPA issues testing guidelines for microbial pesticides ("Subdivision M" of the Pesticide Assessment Guidelines); Subdivision M updated in 1989 after a Scientific Advisory Panel review
- It is in this Subdivision M that the **Tiered testing system** is defined and scientifically justified

Safety...

Human and environmental safety evaluation **Safety studies** Safety Authority evaluation Omics analysis – genome & biological chemistry Application Optimization In vitro and in planta characterization Efficacy Registration & Field performance profiling positioning field trials Stability Stability studies Commercial **Production Strain & Fermentation** Quality Process scale-up Discovery & Research Development Commercialization

Intellection Property – Protecting your investment



Safety studies to prepare for regulatory submission package

The Tier I "six-pack", for microbial pesticide registrations at EPA

- Acute oral toxicity
- Acute dermal toxicity
- Acute inhalation toxicity
- Primary eye irritation
- Primary dermal irritation
- Dermal sensitization

US EPA Tier II Tests - Toxicology

When are Tier II data required (per US EPA)?

"(Tier II) Data required when significant toxicity, in the absence of pathogenicity and significant infectivity, is observed in acute oral, injection, or pulmonary studies (Tier I). Route(s) of exposure correspond to route(s) where toxicity was observed in Tier I studies. The toxic component of the TGAI is to be tested."

[40 CFR 158.2140]

Data Requirement	Test Substance
Acute toxicology	TGAI, "toxic component"
Subchronic tox/path	TGAI, "toxic component"



US EPA Non Target Organisms and Environmental Fate

For Microbial Pesticides

Avian oral toxicity

Avian inhalation toxicity/pathogenicity

Wild mammal toxicity/pathogenicity

Freshwater fish toxicity/ pathogenicity

Freshwater invertebrate toxicity/pathogenicity

Estuarine/Marine fish testing

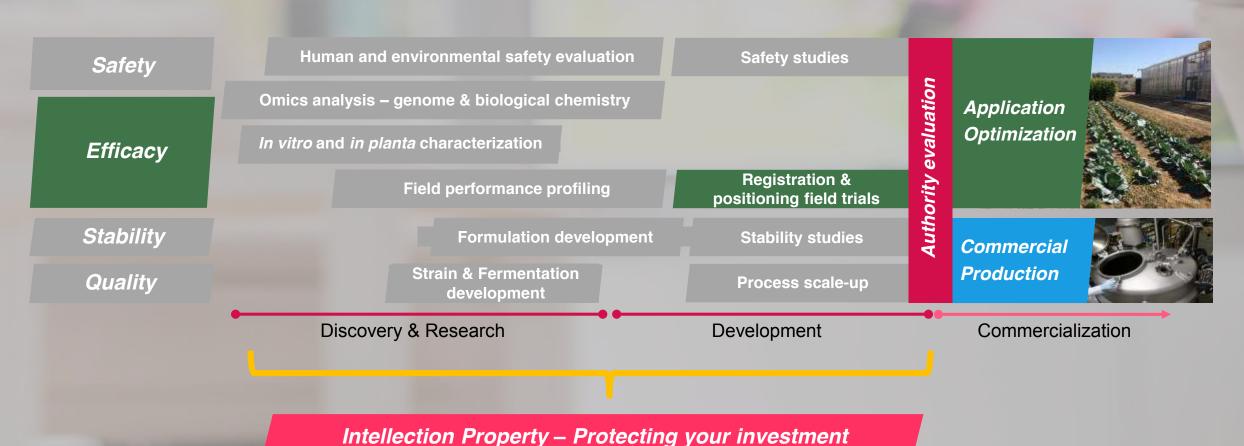
Estuarine and marine invertebrate testing

Nontarget plant testing

Nontarget insect testing

Honey bee testing

Efficacy during Development Phase





Efficacy during Development

Registration trial protocols depend on country

REGISTRATION:

US EPA, trials are not required to be submitted This differs state by state – California requires efficacy

Typically registration trials require stand alone treatments compared to Untreated and standards

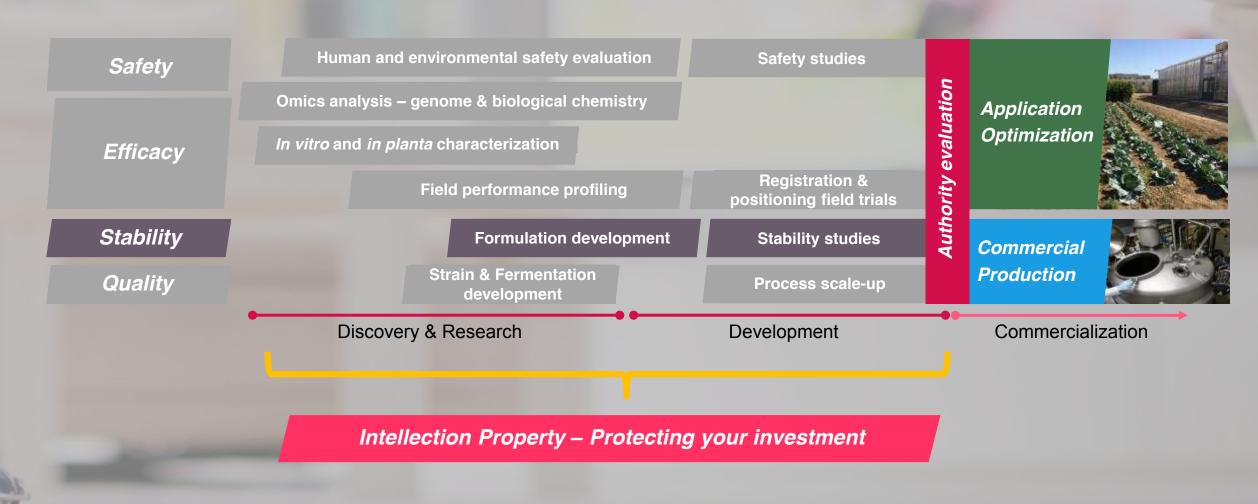
POSITIONING TRIALS:

How will the product be used by a grower? In a program, rotated, tank mixed?

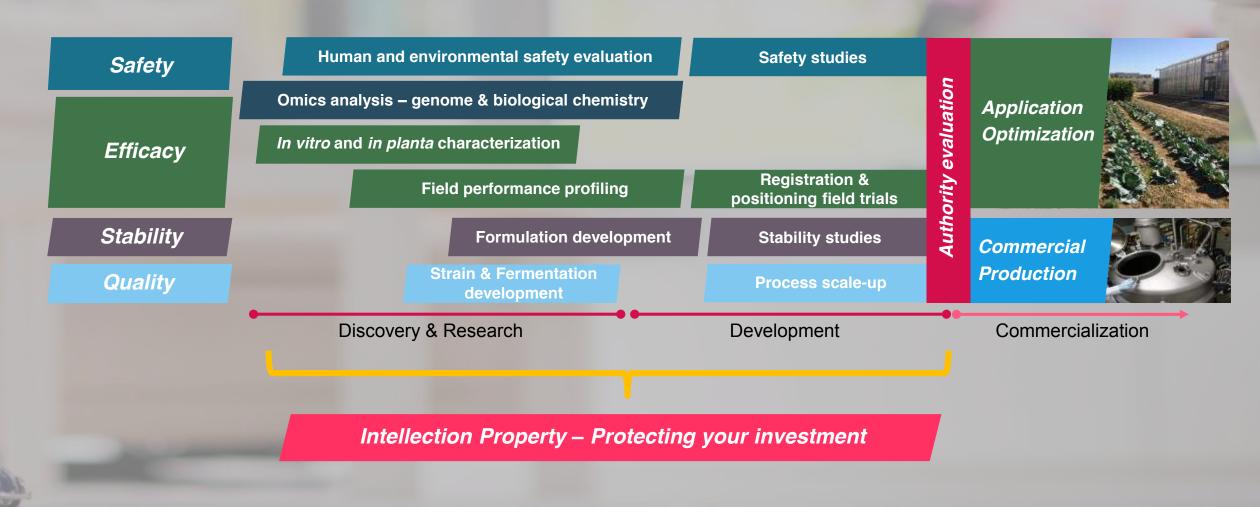




Stability studies also required for Regulatory package



Many steps from idea to market to deliver consistently performing biological products to growers



	The Microbial Curation team manages and
	maintains a diverse set of microbial species in our Biostore.
•	The Computational Life Sciences group mines the strain collection for genes of interest.
Discovery	Pest and Disease Management evaluate the microbes' ability to control plant diseases and pests.
	Crop Efficiency investigates beneficial interactions of microbes with plants, such as increased yield.
•	Strains that show potential to control pests and diseases, or increase yield are selected for higher-tiered testing and further evaluation by our collaboration-focused project teams
	Chemistry analyzes strains of interest to determine What is contributing to the desirable activity and develops assays to quantify these actives.
Strain Research	Microbiology optimizes the selected microbe, identifying variants with enhanced performance.
	Biological activity is measured and confirmed in Pest and Disease Management assays.
	Our Greenhouse team produces plants to be used for testing against diseases/pests in the lab and supports all plant-based research conducted in the greenhouse and microplots.
Process Development	Fermentation develops robust, cost effective and scale-able fermentation processes through media and process optimization at scales ranging from 4 mL to 100 L. Formulation Technology develops processes to concentrate, stabilize and formulate the material to
	create an easy-to-use end product for growers. Human and Environmental Safety evaluates the microbe and formulation to ensure safe use of the
	product concept for humans and the environment.
Field	Agronomic Development tests product concepts in the field.
Development & Regulatory	Our teams here at Bayer Biologics work with our Bayer colleagues worldwide to translate extensive lab and field trial data into a robust and effective product concept that meets growers' needs.
	Regulatory Affairs develops the strategy and data required to obtain and maintain our license to sell by securing registrations with regulatory authorities.
	Potential products are further refined and developed by the Manufacturing Science & Technology team. This includes scale-up in the Pilot Plant to test and
Manufacturing	develop optimal conditions for a microbe before transferring the process to large-scale production.
& Commercialization	Analytical Services ensure quality and safety of our products by testing each batch for consistency and then transfers these methods to the production site.
	Our final product is grown in Production Supply Sites at volumes of 30,000+ liters.
•	Commercial Sales and Marketing teams collaborate with our stakeholders and customers, such as distributors and growers, to help them use these products in their full program portfolio.

Discovery is an exciting and important first step...

But there are many more to follow



Thank you for your attention!

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