The Fascinating Journey from Discovery to Product

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Bayer, Biologics

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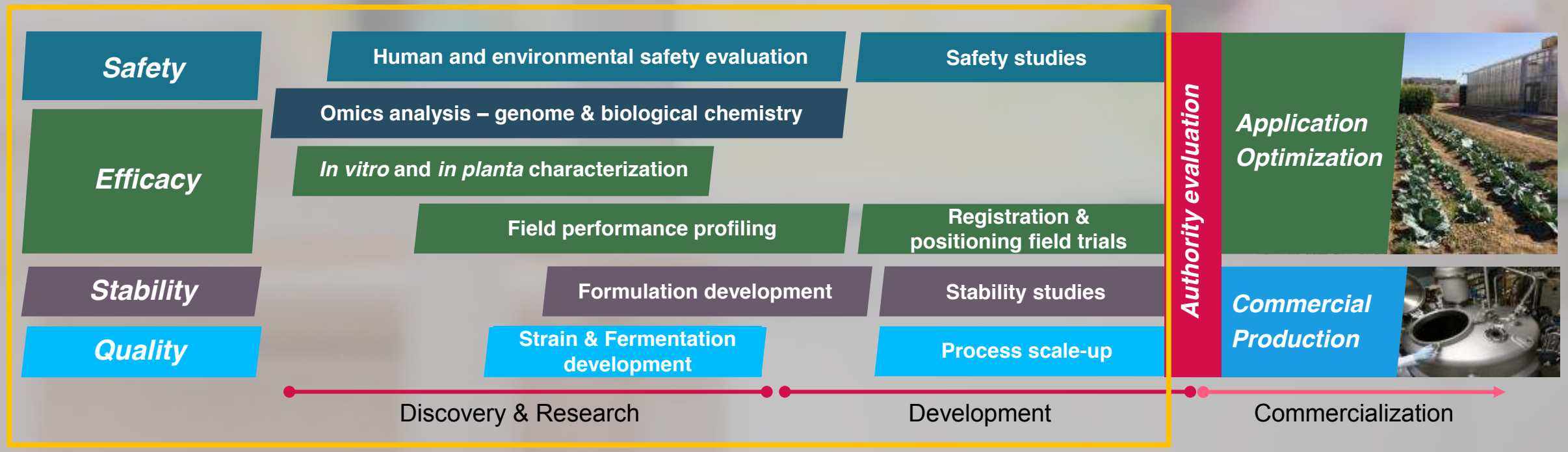
From idea to market, there are many steps to get to a consistently performing Biological product

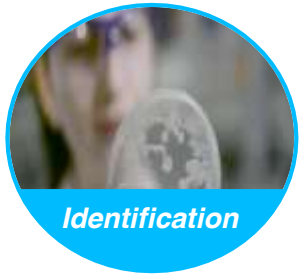


Biostimulants	US	Focus on Corn	+ Years	Total $ ten's of millions Local integration of 3rd party products
	LATAM	Focus on Soybean	+ to +++ Years	
Biocontrol	US	Focus on Horticulture	++ to +++ Years	
	EU		+++ Years	

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?

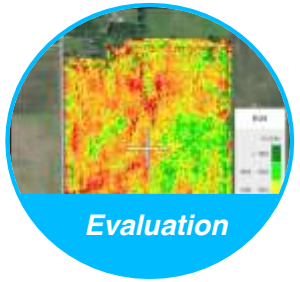
Discovery and Research



- Discovering a lead is the first step in the process

- 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

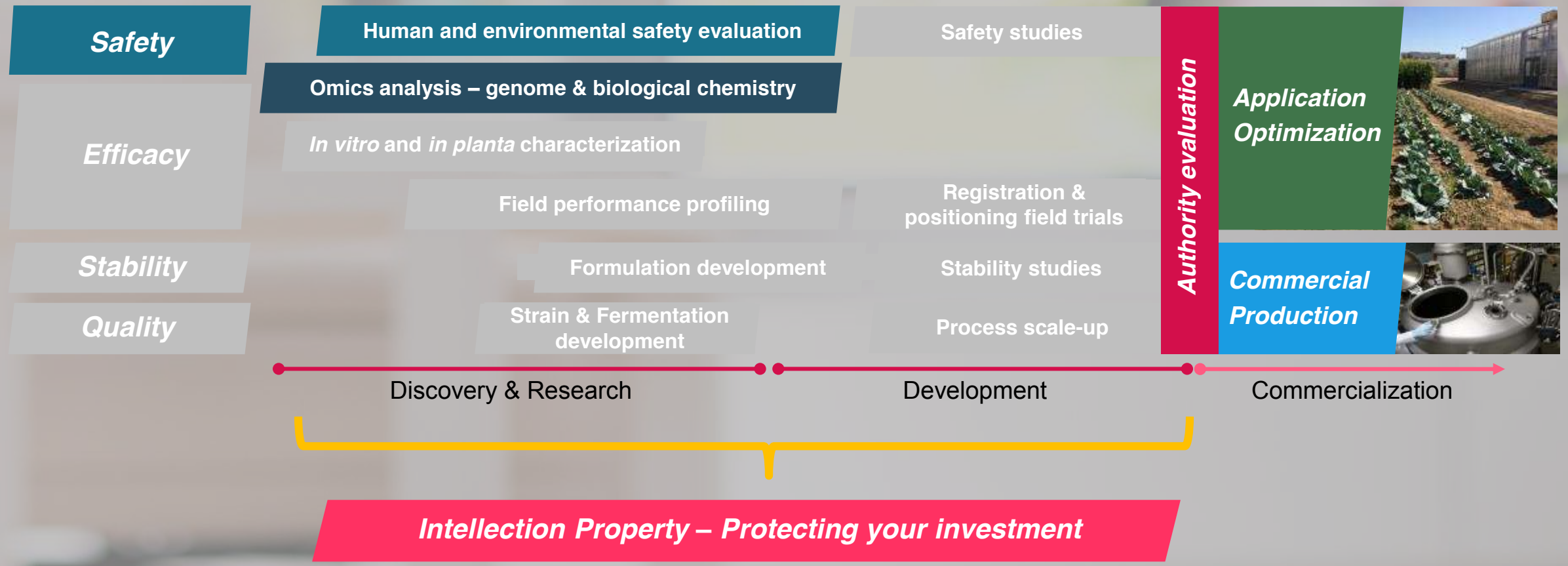
Field Testing

- Registration trials
- Positioning trials

Moving towards Commercial

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

Safety in the Research Phase



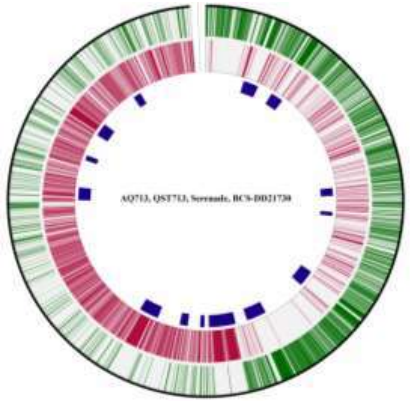
Safety during Research phase

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

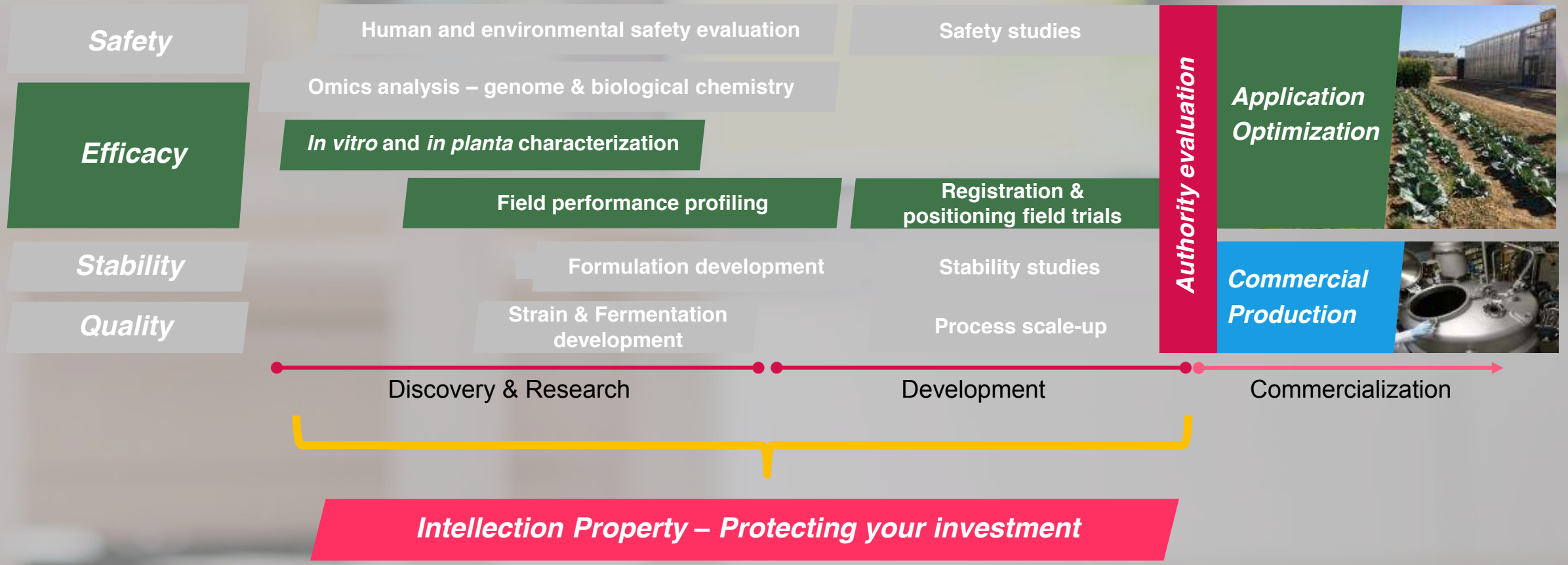
Before we go to field or scale up a fermentation process…

- Non-GLP mouse oral tox?
- Some countries require bee testing before any field trials

Have we determined Plant Safety (phytotoxicity)?



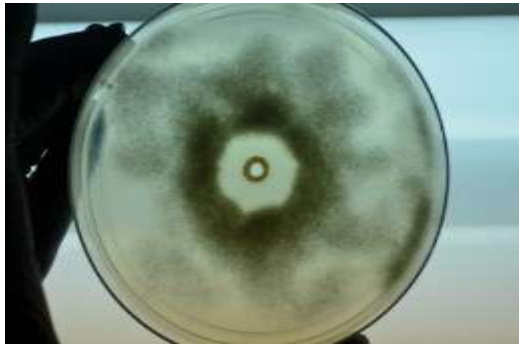
Let’s focus on Efficacy…



Characterizing Efficacy

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

Primary in vitro screening



Screening on plants

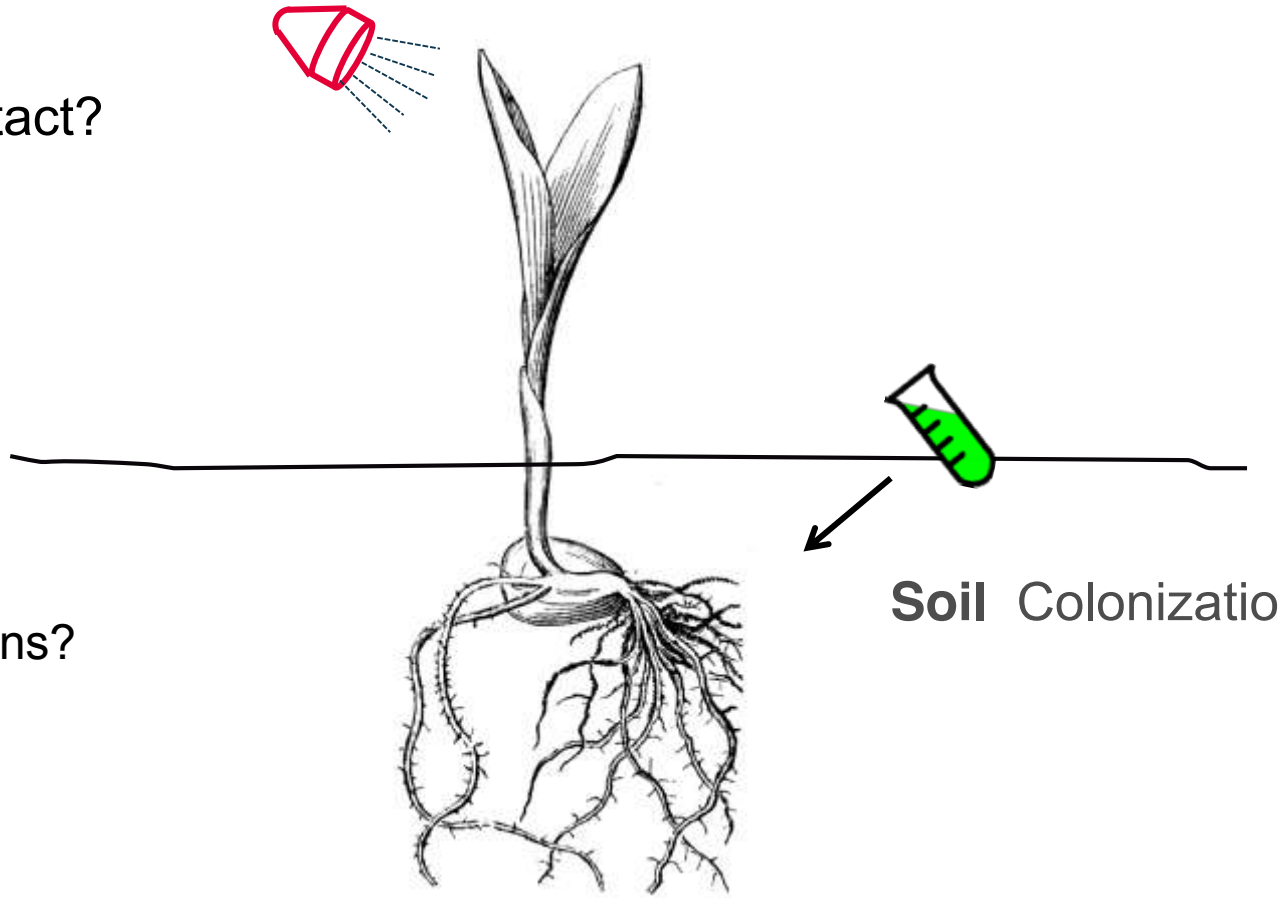
Field Trials on final target

Photos from Bayer Crop Science, West Sacramento

Understanding mode of action aids in field transfer

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

Foliar Contact?



Soil Colonization?

Environmental conditions?

Efficacy during Research

Proof of Concept – moving to the field

QUESTIONS TO ADDRESS:

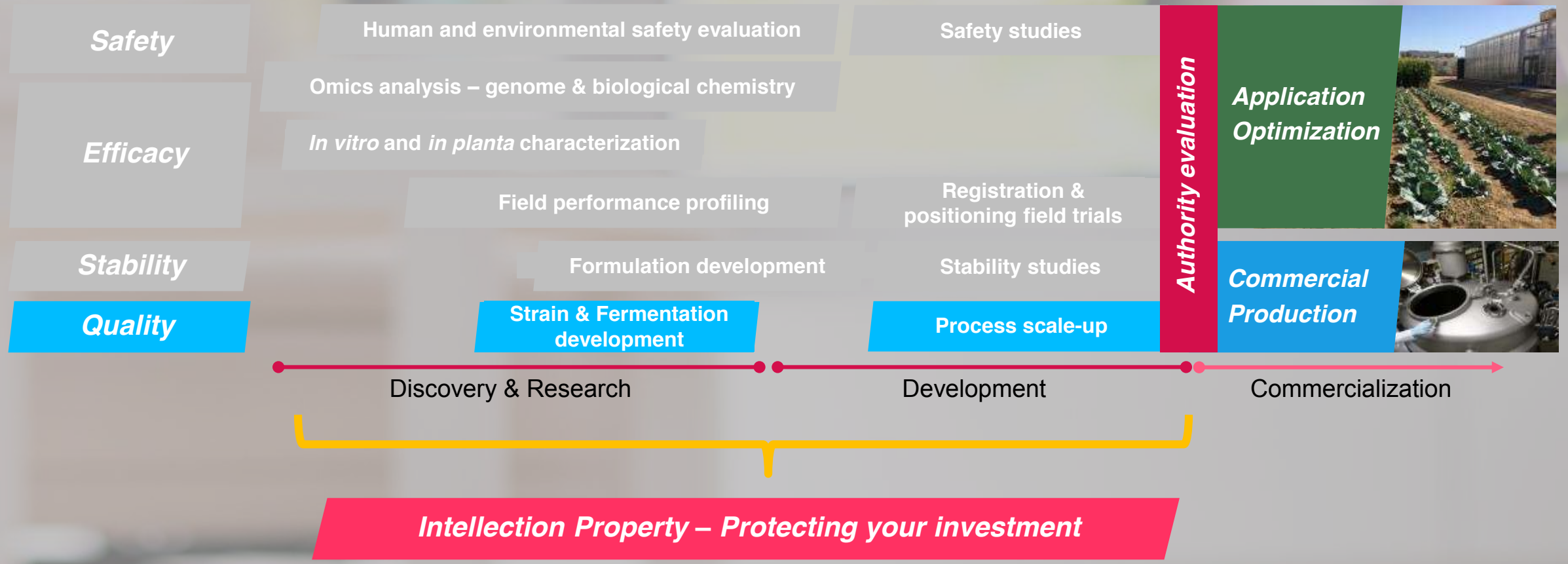
- Best crop and target based on research results
- Efficacious dose
- Spray intervals needed
- Can adjuvants help?
- What are the right controls?

Field trials, what's important

Proof of concept, stand alone, programs

Regulatory trial

Quality and profitability or cost of goods (COGs)



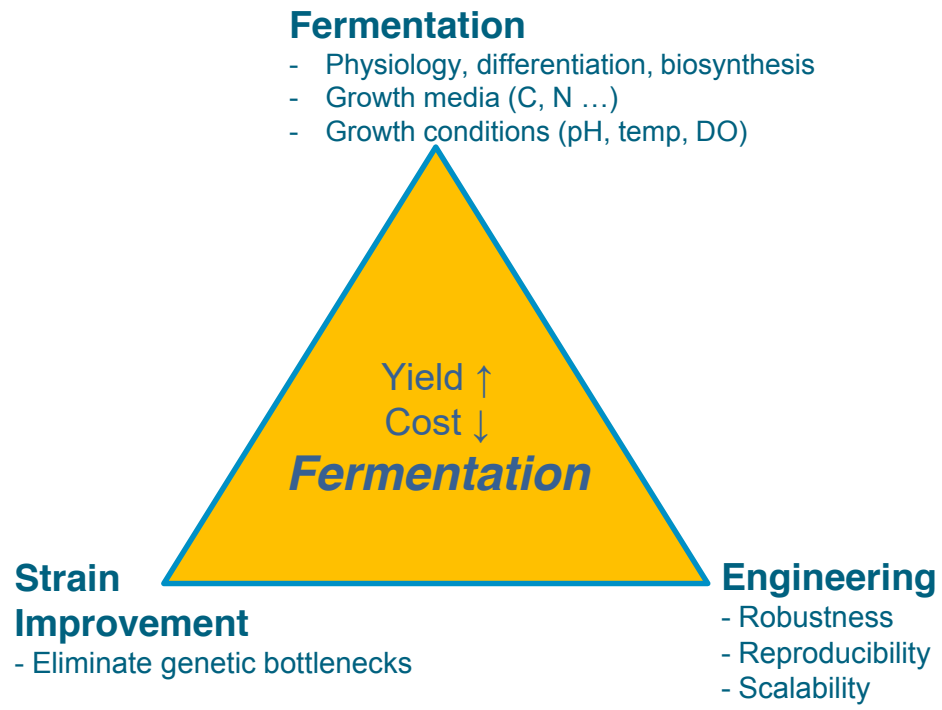
Biological Process Development

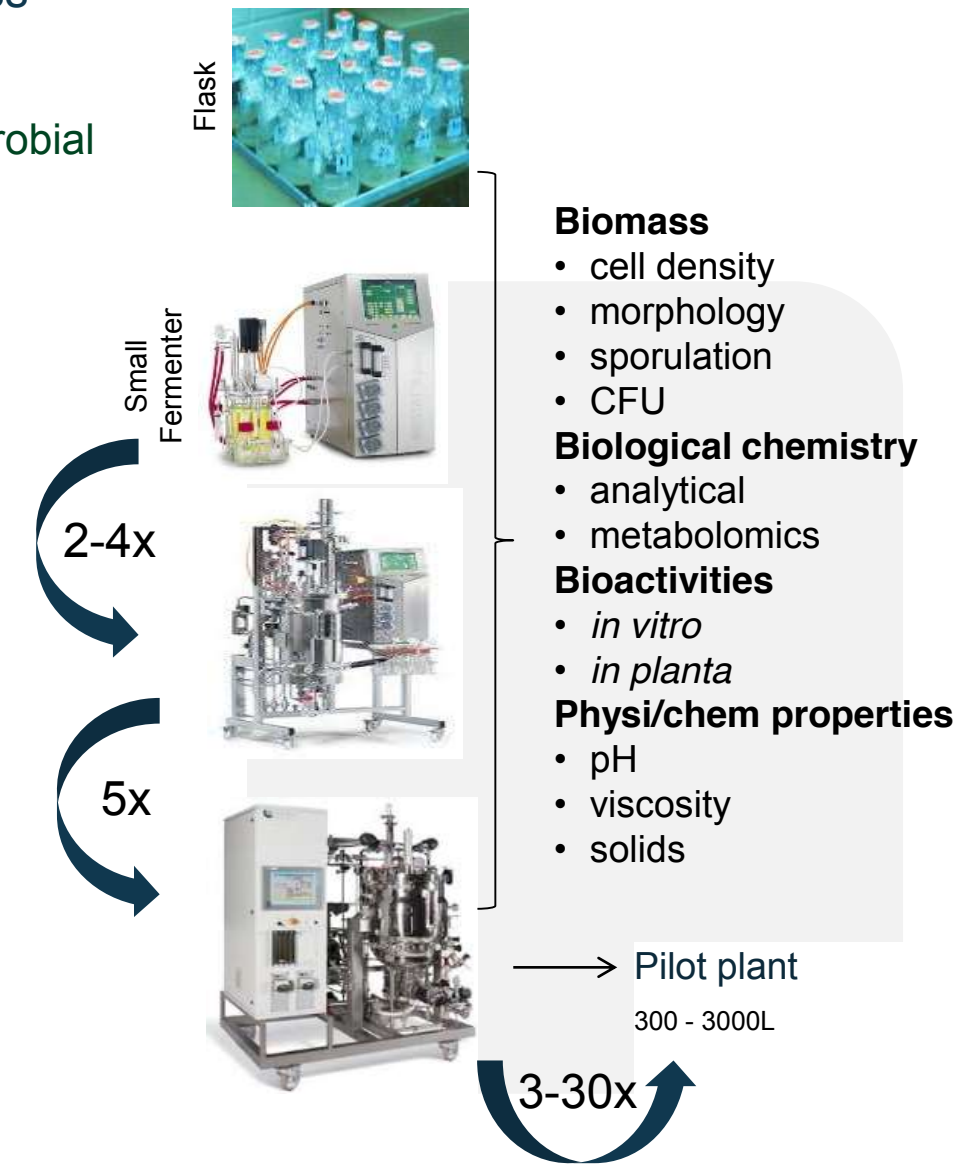
Integrated Approach to Developing a Microbial Fermentation Process

Goal:

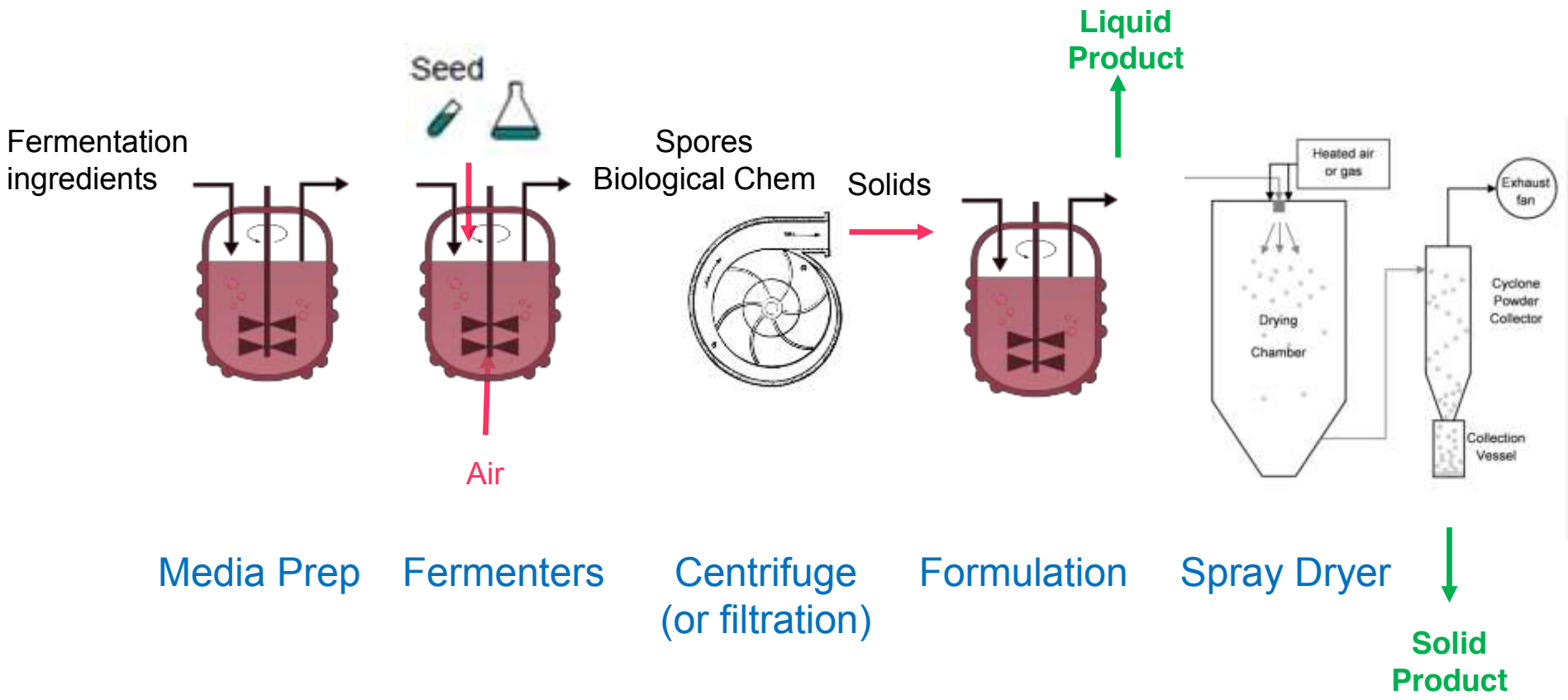
To develop **cost-effective**, robust process for commercial production of microbial active ingredients

Integrated Approaches:





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

10-100x

10-100x

Lab scale

Creation
Innovation
Optimization

Pilot scale

Scale up
Validation
Specifications

Production

Implementation
Reproducibility
Production

Process Development

Transforming microbial discoveries into commercial products

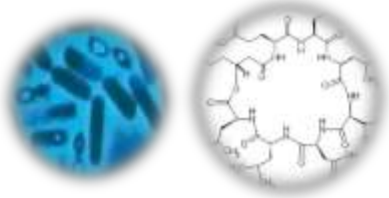
Create manufacturing process & formulation

Fermentation

Downstream

Formulation

Active Ingredients



Concentration/stabilization

Final product

How to interest a partner in development and commercialization

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

Discovery & Research — Development — Commercialization

Intellection Property – Protecting your investment

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…

Safety

Efficacy

Stability

Quality

Human and environmental safety evaluation

Omics analysis – genome & biological chemistry

In vitro and *in planta* characterization

Field performance profiling

Formulation development

Strain & Fermentation development

Safety studies

Registration & positioning field trials

Stability studies

Process scale-up

Authority evaluation

Application Optimization

Commercial Production

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]

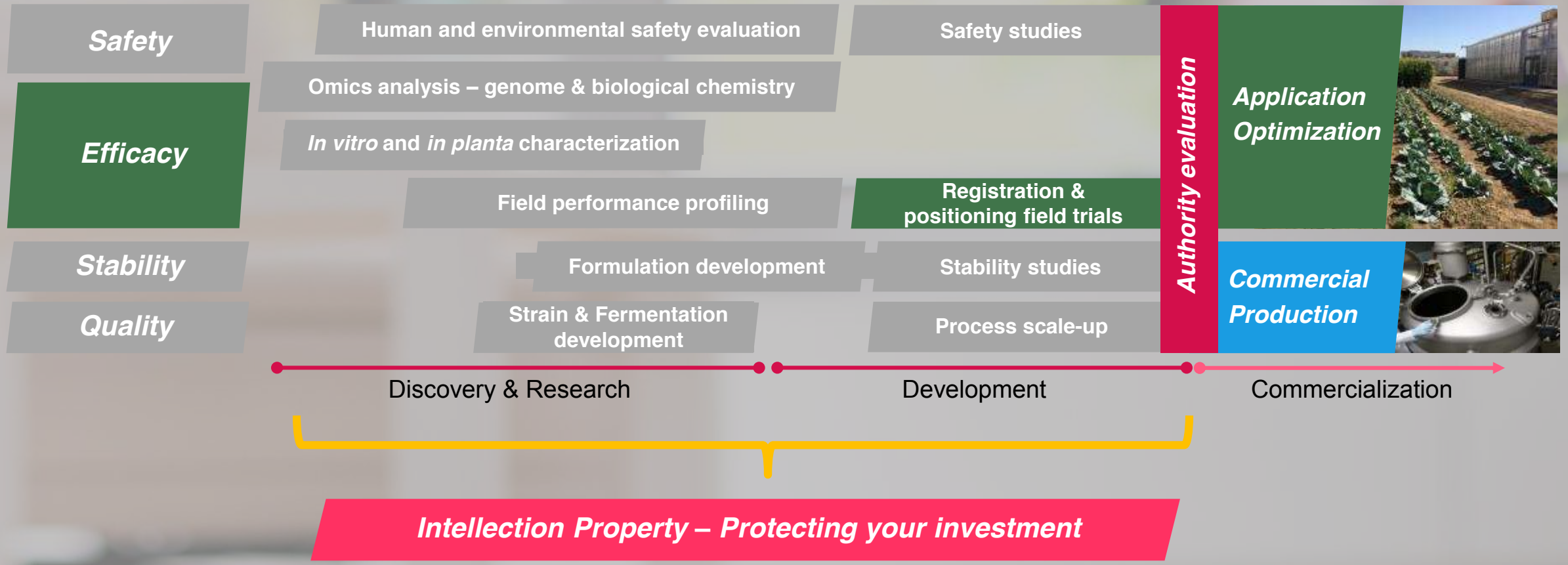
Data Requirement	Test Substance
Acute toxicology	TGAI, "toxic component"
Subchronic tox/path	TGAI, "toxic component"

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

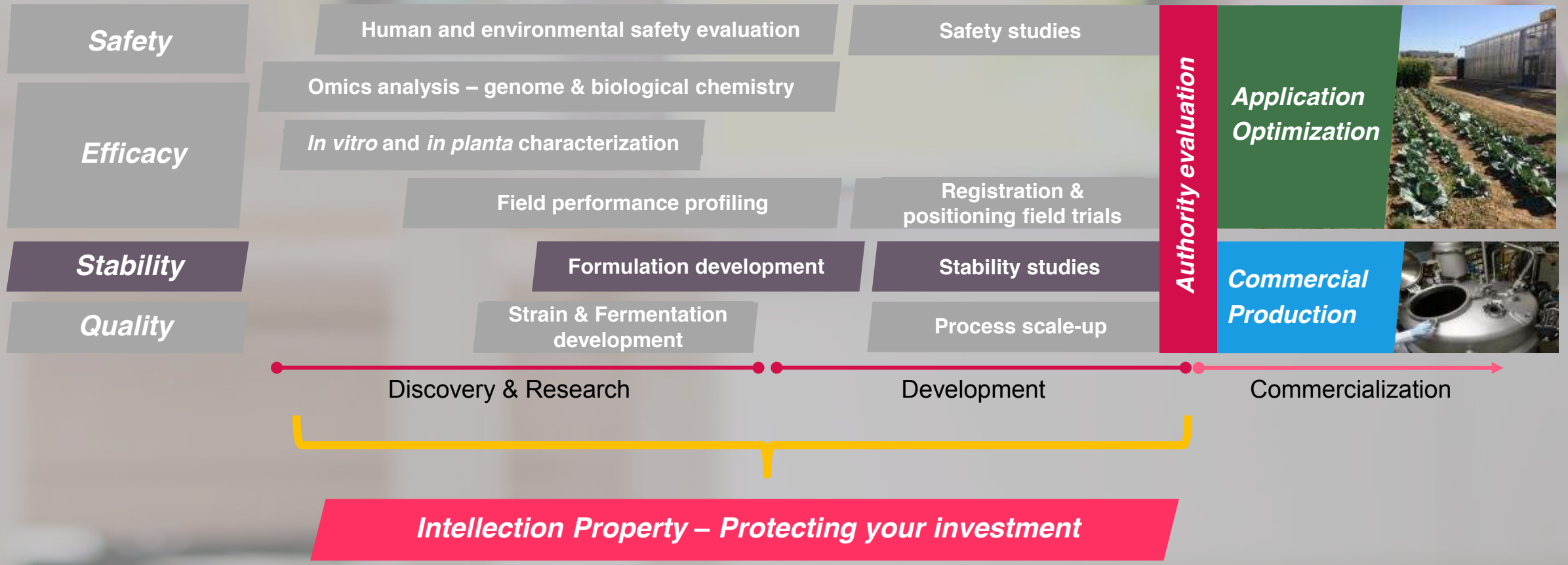
Registration trial protocols depend on country

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

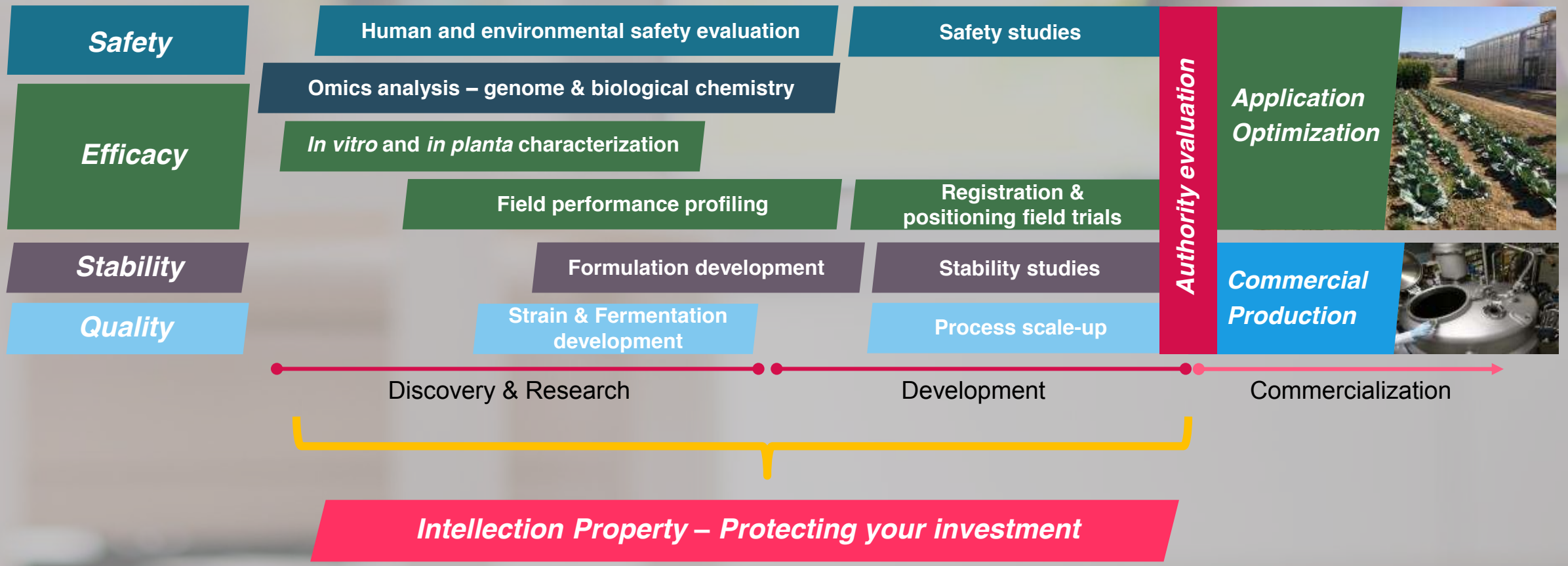
Typically registration trials require stand alone treatments compared to Untreated and standards

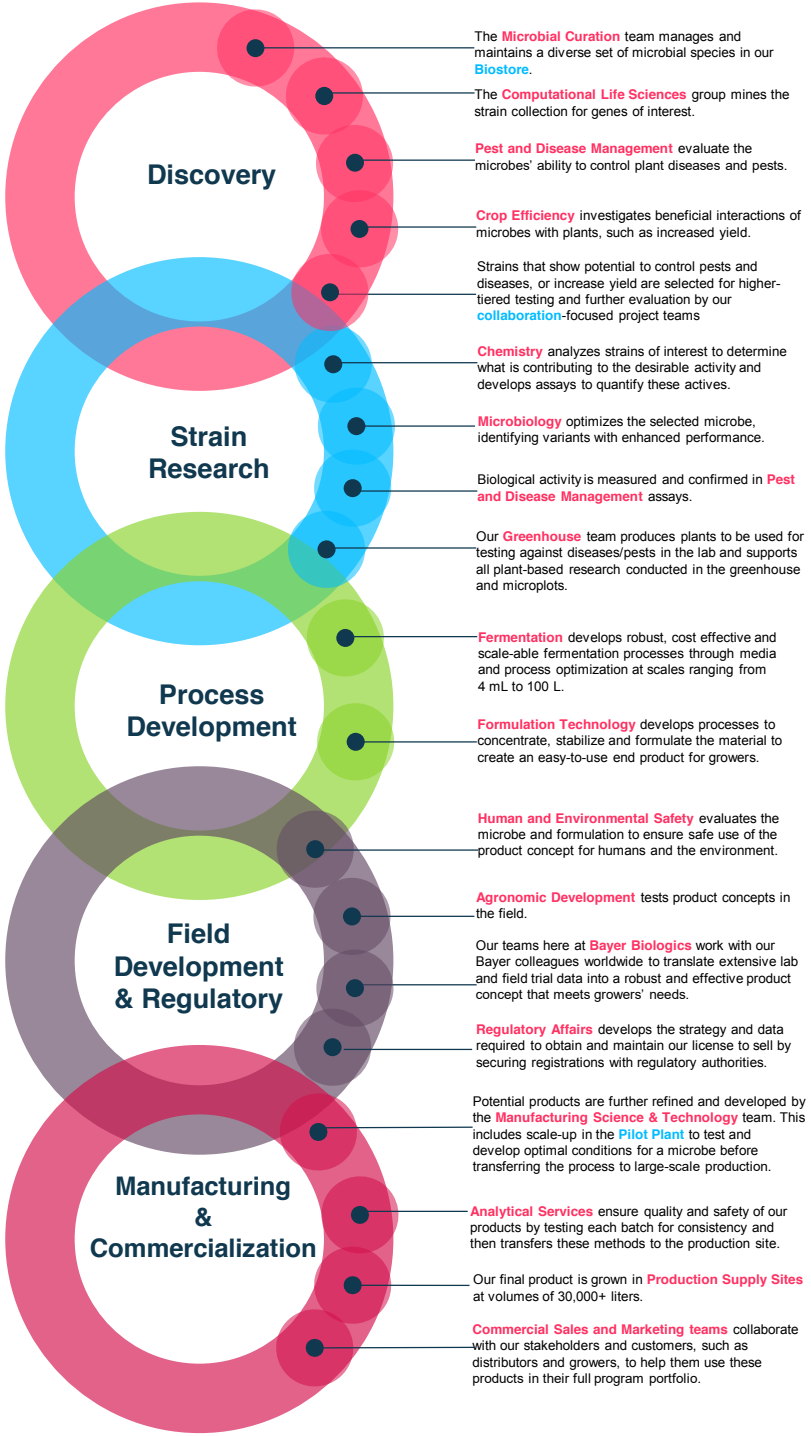
POSITIONING TRIALS:
How will the product be used by a grower?
In a program, rotated, tank mixed?

Stability studies also required for Regulatory package



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





Discovery is an exciting and important first step…

But there are many more to follow

Thank you for your attention!

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