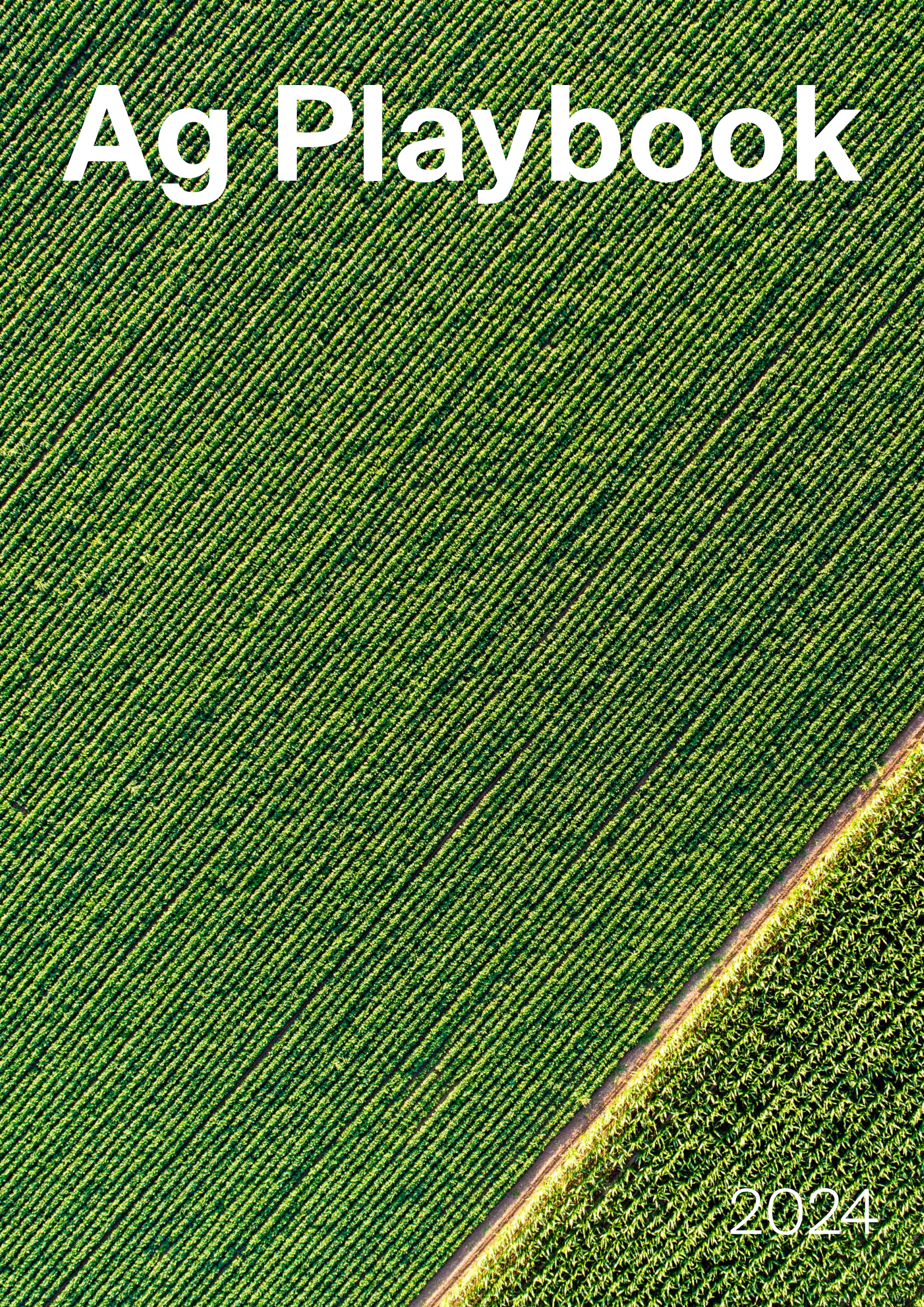
Ag Playbook



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Contents

Introduction

“So, what data can you share to prove that your product works?” “What was your control group(s)?” “How many acres or fields did you replicate your results on and at how many locations?”

Ultimately, at some during every startup pitch or in subsequent diligence, some variation of these questions surface, and unfortunately the answers that follow can often leave the asker wanting. The truth today is that startups have no one-size-fits-all process for agriculture product development. This has led to misuse or misinterpretation of data, anchoring on the hype of an early result, missing a key testing milestone, marketing the potential outcome rather than product, and ultimately under- and over-valuation of early-stage technology companies, putting their innovations at risk of never making it to the market.

The importance and need for innovation in agriculture cannot be overstated. But evaluating that innovation, especially in its pre-commercial stages, requires a common baseline understanding or framework for the product development process. The goal of this document is to deliver a Playbook to help startups, investors, and industry think about what stage a product is at in its development and understand and plan for the cost and effort needed to bring it to market. In doing so, this Playbook aims to aid the efforts of AgTech entrepreneurs so they can more effectively bring the next generation of ag solutions to sustainably feed the world.

Methods & Review

This Playbook is the result of contributions by numerous experts who have worked deeply in the field of agriculture R&D and product commercialization. The opinions expressed here are the individual's own and do not reflect the view of their employer(s).

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The Problem[1]

Bringing a novel agricultural technology (AgTech) product to market is hard. Over the last 10 years we've seen hundreds of products enter the commercial market and into the toolkit for crop farmers. However, a large percentage of these products came from five large agricultural companies (Bayer, BASF, Syngenta, Corteva, FMC) who have spent billions in discovery, development, securing regulatory approval, manufacturing, and ultimately selling these solutions in the market. This is a high bar to set for AgTech startups. If startups plan to follow the conventional industry approach, they will need additional capital, manpower, and expertise to develop and deliver a new product. This makes startups turn to venture capital investment to fund the stages of R&D until they are ready to commercialize their innovation. The AgTech sector is not unique in its use of venture capital, however, it has yet to achieve a common understanding across innovators, funders, and established players of the time and cost it can take to support new products. Once a product is finally ready for commercial launch, AgTech startups encounter a second problem in trying to scale the solution: it becomes clear that getting onto one, ten, or a hundred million acres is very costly, unless the startup partners with other agricultural companies and retailers. Without leveraging the network and existing customer base of these partners, it can be difficult and prohibitively costly to reach the farmer customer. This is the **Reverse Field of Dreams** scenario: "If you build it, the market will not necessarily come."

In short, there are two central problems: 1) the time and cost it takes to develop agriculture products and 2) the difficulty of reaching sufficient customer numbers absent partnering with existing incumbents. Given these challenges, what are the appropriate milestones and inflection points for investors and startups? This Playbook is aims to address the first problem.

Take crop protection small molecule products as an example (not including any of the RNAi or peptide-based products). From 1995 to 2019, the cost of developing a small molecule product increased by 99% from $152m to $301m and the path to market lengthened from 8.3 to 12 years [1]. It now takes even longer to take a potential product through the process of hit finding → lead optimization → toxicity screening → greenhouse/field → regulatory trials → market development trials. Even with the acceleration of discoveries of new hits through use of artificial intelligence (A.I.) and computational platforms and tools, we still see the time it takes to get to market extending due to growing requirements from regulatory agencies. Additionally, there is the time it takes to partner with farmers, academics, trade groups, and established companies to ensure that you achieve not just efficacy but also **belief**. Belief, in this case, is defined as customer acceptance and success. Even if a product makes it through the R&D pipeline, farmer adoption is not guaranteed without industry trust. Farmers operate a high-risk, single decision-point business each growing season that can make trusting a new product difficult. Belief in a product's potential is essential in the AgTech market and is a critical factor in determining which products find success or failure.

[1] Please note that much of the problem statement revolves around plant agriculture. While many of the challenges are similar in animal agriculture, the examples used have been simplified to solutions for crops.

What's different between AgTech & Tech?

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Not all products and product pathways in agriculture follow the same process, but the example above of crop protection small molecule products demonstrates the general trend in the industry of increasing cost and time to market. Developing novel and efficacious products for agriculture is difficult. Safety and regulatory approval are paramount for these products, and unfortunately the digital startup method of building minimum viable products doesn't apply. In the regulated product market of AgTech that often requires government agency approval prior to marketing, the metaphor of "building the skateboard" and delivering it to the market then getting feedback before building the "bike," and ultimately the "car" is not viable, especially when rigorous regulatory testing needs to be conducted and reviewed to support product registrations. In the case of new pest control technologies, products follow a path where they are tested in the lab, growth chamber, and greenhouse prior to being tested in the field. Each phase of testing allows for efficacy and spectrum of control to be tested safely but delays the time to market. The volumes of material needed to test at even the early phases often require access to mini or pilot scale manufacturing capabilities. This means practically, it may be years into product development before investors receive their first actual in-field data or user feedback on results.

What's different between AgTech & Pharma?

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There are parallels between the R&D pathways of AgTech and pharmaceutical (pharma) products. Like AgTech, pharma is a highly regulated market, with the Food & Drug Administration (FDA) and its equivalent global organizations playing a paramount role in ensuring the safety of products brought to patients across the world.

However, there are **five primary differences** when comparing AgTech product development to pharmaceutical product development (taking a US centric view below):

1 Regulatory complexity

AgTech is much like Pharma in that, it develops regulated products that require the approval or consultation of government agencies. In the U.S., depending on the product type, approval by the Environmental Protection Agency (EPA), and United States Department of Agriculture (USDA) may be required in addition to state agency registrations. The U.S. Fish and Wildlife Service (FWS) also enforces national policies around product safety associated with the Endangered Species Act (ESA). Depending on product type, like Pharma, FDA approval or consultation may also be needed. But it doesn't end there. Many ag products are traded in international commerce, so national import approvals are often required in countries where the commodity will end up in addition to the local approvals required where the products are initially grown. Today there is a still variation amongst the testing protocols for different national agencies adding complexity to international scale-up.

2 Seasonality

Each growing region has a limited timeframe when crops can be successfully planted, grown, and harvested, driving the patterns of supply and demand for agricultural products. In AgTech R&D this also means there is limited time when new products can be field tested. Most geographies north or south of the 30° latitude lines have a single main growing season, with planting in the spring and harvesting in the fall. This translates to one chance a year to test a new product during the growing season in those geographies. Researchers can innovate around this limitation by running counter-season programs in northern and southern hemispheres where the seasons are staggered or by conducting research trials in geographies that have multiples seasons (e.g. Mexico). However, if a researcher discovers a new product for the North American market in October, they will likely have to wait six months before beginning a field trial. The impact of seasonality can be very challenging for many early-stage companies working on AgTech innovations.

3 Quick on efficacy, slow on safety

Initial testing for efficacy can be far quicker on the agriculture side, particularly for crop protection products due to being able to test target species such as weeds, insects, and fungi quickly. A scientist looking to develop a novel form of pest control can quickly determine if a crop protection product is affecting/inhibiting growth of the target. However, AgTech products also must prove their effect (or lack thereof) not only in the target organism, but also in a wide array of non-target organisms found in the environment as well. While Pharma products are also tested in non-human species, AgTech product safety testing requirements extend into a highly diverse species set including crop and native plants, mammals, birds, insects, and reptiles.

4 Belief through engagement

Engaging directly with the farmer who buys the product is required in AgTech. Farmers make independent and informed decisions and are not limited in their product access the way patients may be with many Pharma products due to needing insurance coverage and a doctor prescription. Farmers are highly knowledgeable of product offerings and their business needs, engage expert agronomists, and are looking for consistent data and results that support product performance. Because of the wide variability in fields, weather, and agronomic practices, engagement early on to share efficacy and safety to build belief is critical for a successful product launch. Working with groups like the United Soybean Board (USB), National Corn Growers Association (NCGA), Western Growers Association (WGA), International Fresh Produce Association (IFPA), university and USDA ag extension services, independent crop consultants, cooperatives, and state/regional farm bureaus is key to promoting wider-spread adoption.

5 Having a Playbook

The final difference is that testing and bringing a pharma product to market usually follows a well-known playbook. Hit finding, optimization, ADMET tox, pre-clinical tissue & mouse, larger mammal, Phase I, Phase II, Phase III, and Phase IV trials are understood in pharma product development. Government websites even summarize this [2]. The power of these studies to indicate the stage of product development is acknowledged by investors and entrepreneurs alike. AgTech has lacked a similar common understanding of the stages of its testing and development pipeline. This is due in part to R&D operations and strategy being considered a competitive advantage in bringing products to market, with asymmetric information leading to company valuation differences, as well as the ever-evolving AgTech regulatory landscape.

Even with an established Playbook, pharma product development faces large upfront costs with ranges between $500m and $2B for developing a single drug [3] and significant risk with only about 12% of drugs moving from starting clinical phase I trials all the way to market [3].

AgTech product discovery and development is similar. While the regulatory path and the types of testing are different, there is nonetheless also a long, expensive, and high-risk path to market. Our goal is to demystify that path. Like all playbooks, the expectation is that this document will change and adapt over time as it is adapted to provide guidance towards having evermore successful product pipelines. This document is not meant to be prescriptive, but rather to provide a framework and shared nomenclature around the stages of development for key product classes in agriculture.

The Playbook aims to bring transparency and a shared nomenclature of R&D in agriculture to aid entrepreneur and investor alike in bringing new innovations to the AgTech sector.

What's in the Playbook and What's not?

The first chapter of the Playbook is separated by novel product development areas with a demonstration for each of the types of experiments, trials, and results that investors and regulators may expect from entrepreneurs and companies who are developing novel AgTech products. These are not hard and fast rules and do not necessarily correlate to the funding stage of a startup (Series A, B, etc.), since a company can have multiple products in different stages of development. A rough estimation of costs associated with conducting the experiments is provided to better allow for planning and fundraising strategies going forward. This Playbook is not all inclusive, and regulatory requirements are likely to change over time and vary by country and state. Startups should consult the appropriate regulatory agencies and experts early in their product development to ensure they are planning appropriately and in compliance with the applicable regulations and laws.

Each section will highlight three main areas:

Research Pipeline Map & Summary

Estimates on Time & Cost of Development

Key Questions to Consider & Pitfalls to Avoid

The Playbook
Executive Overview

Developing AgTech products is a long and challenging process, requiring the intersection of multiple scientific disciplines.

The first chapter of this Playbook will look specifically at what it takes to research and develop **crop protection small molecule products**. Future chapters may focus on other forms of crop protection products, crop improvement technologies, biological products, digital ag products, and animal ag products.

Each type of product comes with its own challenges in the discovery phase, but all products need to go through similar development **Scale-up** and **Field & Regulatory Trial** stages that are ultimately subject to seasonal dependence.

Across product categories, meeting regulatory requirements and product concept standards while proving efficacy and safety in broad acre field trials can be challenging. Conducting field trials is often the costliest and longest part of bringing products to market. Generally, there is only one spring planting and fall harvest season for each Northern and Southern hemisphere growing region, and time-to-market will depend on successfully executing the required field trials. This is excluding the multi-season growing regions found between the latitudes 10 degrees north or south of the equator that can be used to accelerate timelines as they can have more than one growing season in a calendar year. In agriculture, delays and setbacks are not measured in weeks or months but years. Ultimately weather and environmental conditions can never be completely anticipated or controlled. This challenge further emphasizes the importance of ensuring proper protocol design to power analysis at the end of any season.

Due to the diversity of AgTech product types and how they are regulated, it is difficult to generalize a single timeline or path to market. **Biologicals** may have a seemingly quick route to market, taking as little as 5 years, but it can be difficult to discern actual product impact distinct from other environmental impacts. **Genome editing** has the potential to provide a more rapid route to market than genetic modification (GMO) technologies, but crop plants with the genome edits still need to be field-tested and introgressed into commercially relevant germplasm to demonstrate the added value. Novel uses of artificial intelligence can decrease the duration of hit finding and optimization steps of **small molecule discovery**, but formulation work and the volume and scale of required field trials expands the later stage costs and extends the time of development.

Each product pipeline faces its own challenges but there are a few consistent truths here to emphasize:

1

It takes time (4-13 years) to bring any of these products to market.

While more money can be raised, more time cannot be created. Having rigorous planning around the seasonality of agriculture, including field and registration trials/studies, is critical to success.

2

It takes significant capital ($50-$400m) to develop AgTech products.[2]

Testing in plant model species can begin rapidly for most product types. However, the capital cost to field test in crop plants at the diversity of locations needed to prove efficacy and crop safety continues to rise. And this is only about the path to develop a product; more costs will come to maintain and grow a product in the commercial market.

3

There is a high burden of testing to prove these products will work well within the integrated system of existing agricultural technologies and practices.

Claims of increasing yield using genome editing technology will need to be validated in commercially leading germplasm in large scale, multi-location field trials. A new crop protection small molecule product will need to fit into a system and avoid antagonistic effects with other commercially applied chemistries to be widely adopted. A biological that has a 65% win-rate is only slightly above random chance and therefore not likely to bring the value necessary to move the skeptical consumer.

4

Working with partners and farmers is key to building *belief* and establishing consumer trust in the market.

As mentioned in the earlier problem section, often in agriculture we see the Reverse Field of Dreams: Just because you build and bring a product to market, does not mean the customers will necessarily come. Conducting field trials with trusted third-party partners and farmers and then publishing these results will support claims of product efficacy. By partnering to conduct trials with farmer engagement groups, test farms, universities, retailers, and long-standing companies with strong product histories, innovators can build a stronger base of trust in the results they are reporting.

[2] Software products may be developed quickly and at lower cost, however, will still be subject to testing, adoption, and integration with existing systems.

Phases of Ag Products
Executive Overview

Phase 0
Product Concept

Phase 0 is the starting point where you will define the problem to be solved, the size of the opportunity, and current solutions to the problem (later this will be your positive control group!). Taking the adage to heart: "If I had an hour to solve a problem, I'd spend 55 minutes thinking about the problem and 5 minutes thinking about solutions." The same mentality should be applied to this phase as it can save time and money down the line. This phase should be heavy in interviews of farmers/customers of a future product.

Examples:

In the case of crop protection small molecule products, this phase includes defining the intended crop, pest/pathogen, and molecular target of interest and understanding the current product offerings and unmet need in the market.

In the case of digital ag hardware devices, this phase includes establishing the baseline for current measurement, labor, or operational practices.

Phase I
Pre-Field Discovery

Phase 1 or the "Pre-Field" phase of product development focuses on demonstrating the efficacy of a novel lab or technology discovery. This often includes screening candidates and advancing leads through rounds of iterative trials, redesign, and testing. This is the proof-of-concept phase where the focus is on identifying the lead candidate or product design and testing it against the product concept. Lead candidates should undergo an initial assessment of any prohibitive safety concerns and researcher should prepare a regulatory engagement and approval strategy. Exiting Phase 1, a product should clearly demonstrate high efficacy under controlled conditions and clear differentiation from existing solutions on the market.

Examples:

In the case of crop protection small molecule products, this would include molecular and pathogen target refinement, candidate screening, hit discovery, structure database and patent search review, and lead optimization for new active ingredients.

In the case of a digital ag hardware device, it would mean prototype development and testing.

Phase II
Early Product Development

This phase focuses on three elements: 1) conduct further assessment of any safety concerns and execute the initial regulatory engagement and approval strategy, 2) review leads for novelty and freedom to operate and implement an intellectual property (IP) protection strategy, and 3) demonstrate consistency in performance in a broader diversity of conditions and locations.

Examples:

In the case of crop protection small molecule products, this would involve completion of ecology and toxicity database screens, formulation development, initial cost of goods assessment, and efficacy proof in growth chambers, green-houses, and small plot field trials.

In the case of a digital ag hardware device, it would mean patent review, and movement from prototype to initial product testing.

Phase III Advanced Product Development

Phase III focuses on refining and executing the regulatory approval strategy, generating the required data for regulatory dossiers, and refining the product concept. Many studies at this phase will need to be executed at certified facilities that comply with testing standards recognized by regulatory authorities such ISO standards, GLP[3], and GMP[4]. Phase III includes improving the cost of production for scale-up, achieving key product safety milestones, and demonstrating widespread efficacy. It also generally includes an increase in the reps and scale of field trials at a wider diversity of locations to confirm product efficacy data generated in earlier phases. Engaging legal and regulatory experts early and often is critical during this phase to ensure freedom to operate and value capture for the product upon launch. In addition, early engagement with farmers/customers and affiliate organizations can lead to much easier Phase IV and Phase V experiences.

Examples:

In the case of crop protection small molecule products, this includes scale-up production of active ingredients and inerts, wider testing in small and large acre field trials, regulatory trials and testing, and advanced formulation evaluation, including packaging and related long-term product stability.

In the case of a digital ag hardware device, it would mean taking the product out to the field for side-by-side testing against the best-in-class standard.

Phase IV Pre-Launch Preparation

This phase will focus on supporting the data packages and dossiers being evaluated by regulatory authorities as well as preparation for the upcoming product launch. Simultaneously, a broad data set should be generated to support future marketing and sales efforts. The focus should be not only on building up the data set but also on implementing a literature publication strategy, creating a product stewardship strategy, and developing an effective go-to-market plan.

Examples:

In the case of crop protection small molecule products, this requires a technical profile for the new active ingredient to be fully defined, that a core formulation concept is established and is free for registration, and that the global dossier to regulatory authorities for the initial key market(s) are complete.

In the case of a digital ag hardware device, it implies widespread testing of the hardware in various regional, soil, weather, and time conditions to ensure its broad use. This is also where workflow analysis can best be tested.

Phase V Launch and Market Expansion

This launch phase focuses on continual testing to aid the business development and expansion into new markets as well as the continual improvement of the product for improved efficacy and reduced cost of goods sold (COGS). This phase also includes continuing to work closely with legal and regulatory experts as the product is packaged, labeled, and sold and looking for opportunities to extend the product lifecycle and maintain competitive position.

Examples:

In the case of crop protection small molecule products, this means conducting large acre field trials in new geographies to demonstrate local product performance and developing new formulations and mixtures with other active ingredients to improve product efficacy, COGS, shelf-life, and meet any local formulation requirements for registration.

In the case of a digital ag hardware device, it could mean improving usability, durability, battery-life, or accuracy of the product in question.

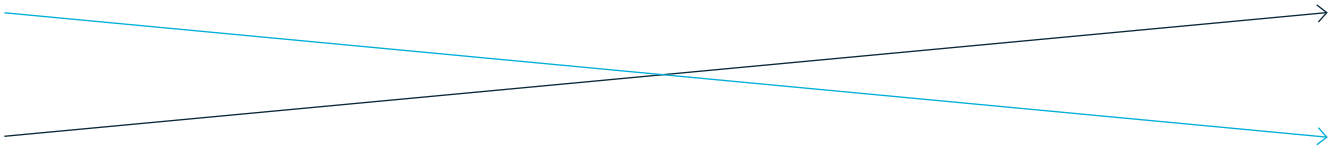
[3] Good Lab Practices

[4] Good Manufacturing Practices

Phases of Ag Products

Phase 0	Phase I	Phase II	Phase III	Phase IV	Phase V
Define the Problem	**Pre-Field Discovery**	**Early Product Develop-ment**	**Advanced Product Develop-ment**	**Pre-Launch Prepara-tion**	**Launch & Market Expansion**
Establish the size of the opportunity Research the current market solutions Extensively inter-view and meet with farmers and customers	Develop a proof-of-concept solution Prove plausibility under optimal conditions Conduct initial IP review and develop regulatory engagement & IP strategy	Assess safety concerns Establish FTO and execute regulatory engagement & IP strategy Demonstrate performance in more geographies	Generate data needed for any regulatory dossiers Prove scalability and drive down COGS Broaden field testing to even more geographies and test with partners	Finalize regulatory dossier support and stewardship requirements Scale-up production plan Expand market development field trials and develop go-to-market plan	Lower the COGS for production Extend product life-cycle Continue testing to expand into new markets

Risk of products success



Cost and time

not 100% linear

Estimates on Time & Cost of Development

There will be variation across product classes when estimating both the time to market as well as the cost of development. With that acknowledged, this Playbook will use a simple calculation principle for estimating time and cost.

$$\textbf{Time} = \alpha_T + \beta_T$$

$$\textbf{Cost} = (\alpha_c + \beta_c) * (1+\gamma)^{\delta}$$

Where:

α_T = Last reported time for product development
α_c = Last reported cost for developing a product
β_T = Time impact of key research or development trend
β_c = Cost impact of key research or development trend
γ = 2.73 = 10 year inflation rate average
δ = Avg number of years since last reported cost of developing a product

Crop Protection

Disease, Insect, Nematode, and Weed control technologies

Includes seed treatment, in-furrow, or foliar-applied solutions, as well as genetic traits that are used to control pests, pathogens, and weeds to improve crop performance and yield

Crop Protection Product Types

Small molecules
Peptides
Oligos (RNA, DNA)
Proteins
Biologicals
Genetic Traits

U.S. Regulating Agencies: EPA, USDA
Potential U.S. Agencies to be Consulted: FWS, FDA[5]
International testing guideline resources: OECD & FAO

[5] FDA while not required to launch a product, it will be an important agency in the case of any EPA residue studies showing potential impact in food products.

Crop Protection
Product Nomenclature

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There are many ways to divide up the world of crop protection products. They can be segmented by **application type** (seed treatment, foliar, in furrow, in plant, etc.), **indication** (fungicide, insecticide, herbicide, nematicide, etc.), or **timing of application** (pre-season, mid-season, late-season). For the purposes of the Playbook, we will focus on a segmentation based upon **size**, which also correlates with composition.

The simplified framework below gives a variable range of sizes of each of what we'll categorize as the 4 distinctive groupings:

Small Molecules	**Oligos & Peptides**	**Proteins**	**Biologicals**
			
<1 kDa	5-15 kDa	3-150 kDa	>150 kDa

General Truth:
With an increase in size comes an increase in complexity.

General Misconception:
Because some products have faster paths to market, they will not be as efficacious, specific, or financially viable as the more regulated paths.

Not mutually exclusive:
Final products can contain or be used as a combination of products from more than one group.

Small molecule

Small molecules are a diverse and highly specific group of chemicals that act upon targets (usually proteins) in the cells of organisms. Binding of the small molecule to the target typically leads to the activation or inhibition of that target and its activity in the cell. Small molecules can bind more than one target at a time as well. If we look at PROTACS as an example, these bifunctional molecules bind both the target of interest on one end as well as an E3 ubiquitin ligase on its other end. The number of possible small molecules is enormous and has yet to be fully explored[6]. Small molecules are the most prevalent form of crop protection product used today because they are highly specific to the target(s) of interest, can be synthetically manufactured, and are formulated for shelf stability. The category of small molecules has huge potential for discovering novel products, and we have only scratched the surface of this molecular universe.

Oligos & Peptides

Oligos and peptides are short chains of nucleic acids or amino acids, respectively, that can be synthesized or produced using recombinant methods. Oligos and peptides find use as the active ingredient in many different types of crop protection products including those utilizing single and double stranded DNA, RNA, small interfering RNA (siRNA), and short amino acid chains. Oligo products in this category that induce RNAi have made their way into the agricultural market in the past decade, and to date there have been at least 18 peptide products commercialized for plant protection including the bioinsecticide Spear®, which originated as a neuropeptide of the venom from the blue mountains funnel-web spider. [5]

Proteins

Proteins are macromolecules consisting of amino acids (and any lipid or carbohydrate post-translational modifications) that can be purified from natural sources or produced using recombinant methods. Proteins can act in a variety of ways as the active ingredient in crop protection products. A well-known example are the proteins from *Bacillus thuringiensis* (Bt), which is a Gram positive, spore-forming species of bacterium from which proteins toxic against a wide range of insects and nematodes have been sourced. These proteins have been successfully used as insecticides against caterpillars, beetles, nematodes, mosquitoes, and flies. Formulations containing Bt cultures have been used in agriculture as pest control applications to the surface of crop plants since the 1950's, and GMO plants expressing recombinant Bt proteins have been widely used for pest control in row crops since the 1990's.

Biologicals

Biologicals are products that contain living microorganisms such as fungi and bacteria as the active ingredient. These microorganisms often have highly regulated metabolic pathways to intake and output key products. A study released in April 2023, conducted by the Stratovation Group and commissioned by the Fertilizer Institute and the Agricultural Retailers Association, found that more than one-third of the U.S. farmers surveyed were currently using at least one biological product on their crops [6]. A University of Nebraska overview of biologicals subcategorizes these products into **biostimulants** like plant growth promoting rhizobacteria (PGPRs), which are used to help plant adapt to abiotic stresses, and **biopesticides** like Regalia®, which is used to control the fungal disease powdery mildew.

[6] For context, using the GBD-17 database compilation of the most frequently occurring atoms with Sulfur (S), Carbon (C), Oxygen (O), and Nitrogen (N), if we combine just 17 of these atoms, it would lead to over 177 billion possible molecules. [4] Going one step further and using 24 possible atomic combinations, we'd easily surpass 10^30 different possible molecules, which is more than the estimated number of stars in the universe. Of course, atoms do not randomly link into molecules, so the actual number of atomic combinations is more limited, but it shows the diversity of small molecule opportunities.

Crop Protection
Small Molecules

Disease, Insect, Nematode, and Weed control technologies.

Seed treatment, in furrow, or foliar applied solutions for control of pest pressure and improvement of crop performance

Crop Protection Product Types

Pheromones
Small molecules
Natural Products

U.S. Regulating Agencies: EPA, USDA
Potential U.S. Agencies to be Consulted: FWS, FDA[7]
International testing guideline resources: OECD & FAO

Estimated overall cost: $312-381m USD[8,9]

[7] FDA while not required to launch a product, it will be an important agency in the case of any EPA residue studies showing potential impact in food products.
[8] Based upon small molecule costs, which have the most well-documented registered products.
[9] The initial costs for the analysis here will be reported numbers from the 2024 public publication from AgBioInvestor on behalf of Crop Life [1] which does a great job of breaking down the trends of crop protection R&D cost over the past 30 years from the top agricultural companies

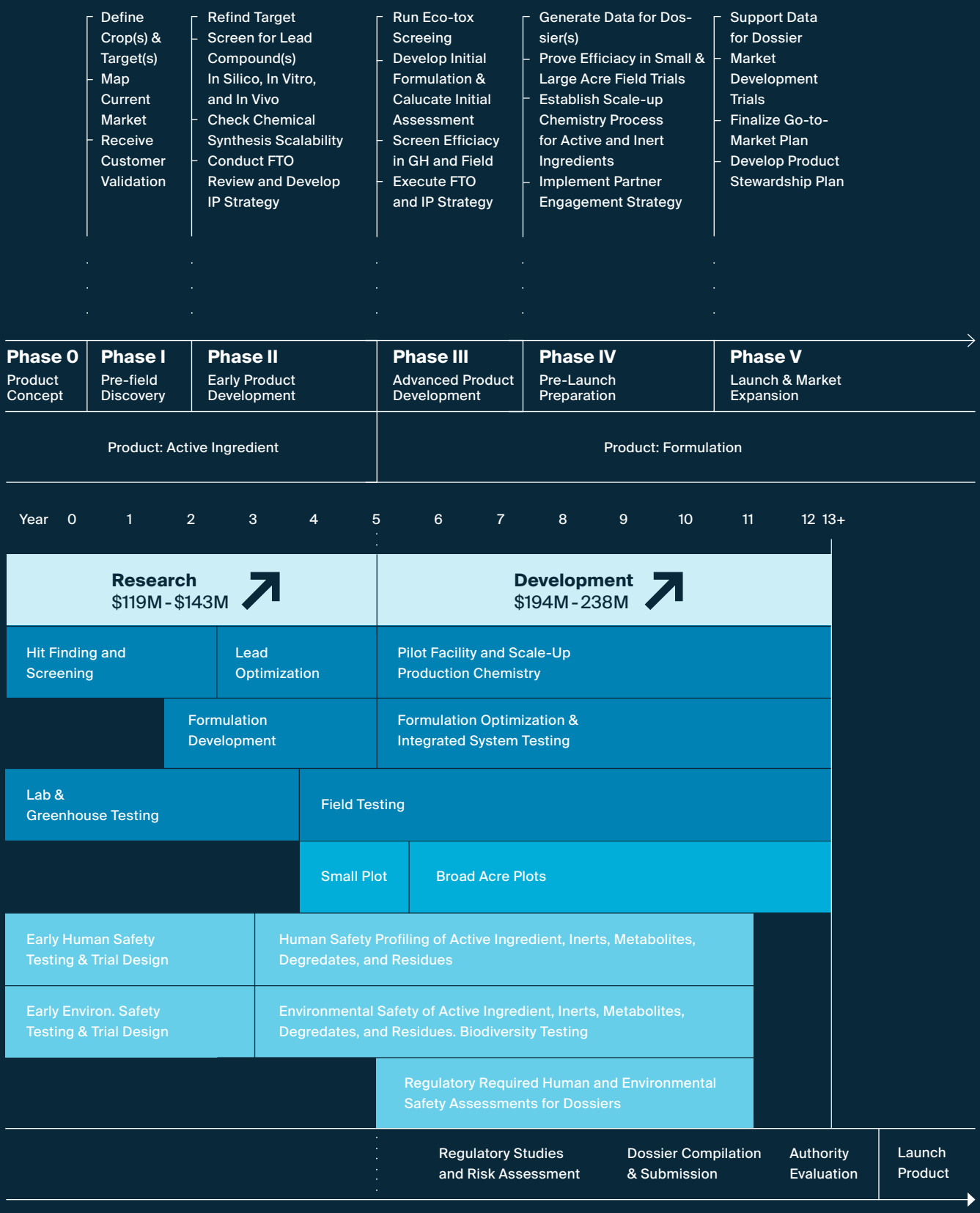
Introduction

Most crop protection products in the market today fall into the category of small molecules. These products are formulated to be used as either seed treatments, in furrow, or as foliar applications to control pests and pathogens including weeds, insects, fungi, bacteria, and nematodes. Crop protection small molecule products represent some of the most impactful AgTech products on the market because of their utility to protect crop yield combined with their specificity, scalable production, and ease of application. The bar to produce these products continues to rise and with it the cost of R&D pipelines. Developing a crop protection small molecule with the highly specific physiochemical properties and safety profile that meets both agronomic needs and societal expectations for safety and environmental protection requires the researcher to consider many factors. Indication, mode of action (MoA), crop segment, efficacy, feasibility of synthesis and production, cost of production, formulation offerings, and safety for humans and the environment are critical attributes for a crop protection small molecule product. The new molecules, like their predecessors, are designed to minimize the potential effects on non-target organisms and the environment according to pre-defined safety and sustainability profiles.

Crop protection small molecule research and discovery can be broken into four basic activities:

Phase 0 – Phase II Research	Phase III – Phase V Development
includes (1) hit finding & screening and (2) lead optimization & formulation development.	includes (3) scale-up of production chemistry and (4) field and registration trials.

Product Pipeline Map (Simplified)



Phase 0 – Phase II:
Research

Hit Finding
and Screening

Phases 0 & Phase I

Timing: 6-24 months

Summary

Target identification is an important part of the early discovery process, and its effectiveness sets the stage for discovering a successful crop protection small molecule. Whether a target has been identified or not, there are two main approaches for discovering small molecules:

Structure-based molecular design: Identifying a specific target to modulate with a small molecule and using computational and combinatorial chemistry techniques to screen small molecules for their potential effect on the target.

Ligand-based discovery: Starting with a small molecule known to have efficacy and using it to dis-cover the target of interest and develop new small molecules with greater efficacy.

The goal is to find novel small molecules (active ingredients) that will effectively modulate a target and cause a phenotypic result.

Opportunities & Common Pitfalls

In Silico ADMET screening allows for better prioritization of scaffolds and chemical series.

Overemphasizing virtual screening without validating both in vitro and in vivo assays. Translating each step from virtual → in vitro → in vivo can be difficult, but important to validate early.

Production costs of any chemistry can become the limiting factor when manufacturing at scale, so finding synthetically facile chemistry improves the chance of making market-feasible product.

Failure to conduct early IP review and develop an IP strategy to ensure freedom-to-operate and patentability of new small molecules.

Cost Range & Trend

$50M-$60M, the highest cost drivers are the establishment of chemical synthesis pathways and the biochemical and biological assays used to rapidly test the efficacy of the small molecule of interest.

Decreasing significantly due to the use of artificial intelligence and computational chemistry tools. These trends mean lower numbers of small molecules must be physically synthesized and tested to find hits.

Please note: These costs are based upon reported numbers from larger ag research companies. Startups that originated their chemistry from academia or focus in a specific chemistry area may minimize much of this early-stage cost.

Target identification is a vital part of the crop protection small molecule research and development process and enables researchers to better understand the **MoA** of potential new active ingredients and optimize the active ingredient for a particular pest or pathogen. Early agrochemical discovery methods relied heavily on phenotypic screens against pests or pathogens of interest. Hits were then studied using extensive genetic, biochemical, and metabolomic methods to determine the molecular target. While this biology first approach still has merit for identifying in vivo hits early in the process, the resulting compounds need to be further screened for undesired activity against non-target organisms and this can lower the hit advancement rate. The target first approach is based on starting with a specific target to modulate in a pest or pathogen and then using computational and combinatorial chemistry techniques to screen small molecules for binding to that target. Target identification is an important part of the early discovery process, and it can enable a higher rate of advancement for crop protection small molecules.

Once a target has been identified, there are several approaches to discover new active ingredients. While there is a wealth of innovation in this space, the most used approaches are structure-based molecular design and ligand-based discovery.

> **Structure-based molecular design** focuses on a game of microscopic Tetris, where researchers attempt to model what molecules might best bind to the target of interest. In most cases the target of interest is the protein's active site or an allosteric site. By binding to these sites, a small molecule can affect the activity of the protein in the pest or pathogen and thus stop it from impacting the crop and reducing yield.
>
> **Ligand-based discovery** leverages existing small molecules known to bind a target of interest and seeks to find similar molecules with improved binding to the same site in the protein or improved chemical properties such as water solubility and ease of synthesis. In this category, researchers need to be mindful of the existing intellectual property rights to ensure any improvements they make are patentable.

Between 1995 and 2014 was the golden age of high throughput screening, where large numbers of compounds were screened to find a single active ingredient that produced the desired response. According to one report, by 2014 developers needed to synthesize and screen over 150,000 compounds to find a single hit [1]. In the last decade, the growth of large, public protein data banks and small molecule databases has enabled focused computational screening, artificial intelligence, and simulation technologies to dramatically decrease the number of compounds that must be physically screened. The use of computational and artificial intelligence tools to mine the large universe of molecular combinations mentioned earlier (over 10^30) has moved much of high-throughput screening from the physical world to the virtual space, so it is quicker and less costly.

Numerous companies specializing in the use of A.I. and computational techniques to accelerate the rate of small molecule discovery have emerged. The utilization of A.I. and neural networks has led to faster and cheaper discovery of potential new hits. Instead of synthesizing and testing tens of thousands of molecules over the span of years, virtual screening has shortened this phase into just weeks and months. Companies can now simulate and rank virtual small molecules and then only synthesize and test a select small number of those molecules. Virtual hit finding has been one of the more compelling uses of A.I. in scientific product development to date. The limiting factor now is the ability to rapidly synthesize and build assays to test the identified potential hits. It is the biology of testing the active ingredient/target interaction that becomes the limiting step in early discovery.

Opportunities & Pitfalls with Hit Finding & Screening

Use of A.I. and simulation in the virtual space has enabled rapid early discovery, however, it further emphasizes the opportunities that still exist in the physical discovery space. The three challenges below highlight recent opportunities in setting up biological assays and producing synthetically facile chemistry.

1	**In silico ADMET screening:**	ADMET (absorption, digestion, metabolization, excretion, and toxicity) screening is important in understanding how an organism will respond to an active ingredient. This is often used in safety assessments. Like hit discovery, ADMET screening models have been migrating to the in silico (virtual) space. In a recent publication, researchers leveraged a deep learning approach to make predictions of 100 ADMET assays, assessing the potential for a compound to become a relevant drug candidate [7]. However, the species of interest in agriculture do not follow the same ADMET rules as those used for humans. This was supported in 2001 by Colin Tice, when he published his results when looking at Lipinski's rule of 5 as it applied to agrochemicals [8]. In silico generated virtual compounds generated through both optimized binding models and ADMET models can allow for better prioritization of scaffolds and chemical series, but the screening parameters will need to be adjusted.
2	**Translating from in silico to in vitro to in vivo**	Translating from in silico to in vitro to in vivo can be difficult but is important to validate early. Testing both in vitro (for example in a 96 well plate or test tube) and in vivo (in a model organism or pest) can be simple and inexpensive in agriculture, but it takes time to design and execute the right assay.
3	**Finding an economically viable chemical synthesis route:**	Chemical synthesis can become the limiting factor when manufacturing at scale, so finding synthetically facile chemistry improves the chance of making a market-feasible product. The chemical synthesis route taken to make the active ingredient for assays and screening in this phase is rarely the final process used for production, but ensuring the active ingredient can be made or bought at a reasonable cost and in sufficient quantities early on improves the likelihood of success.
4	**Conducting an early FTO Review and developing the IP protection strategy**	Ensuring both freedom-to-operate (FTO) and the ability to protect future products will allow for value capture on products and eventual return on investment.

Hit finding and screening has become one of the most technology-transformed research steps in agricultural discovery due to the use of artificial intelligence and automation. This also demonstrates the potential of these technologies to optimize other stages of R&D testing pipelines to become cheaper and faster while remaining equally safe.

EXAMPLE

In silico

An increase in the number of molecules and protein structures made available in public databases has enabled massive virtual screening and prioritization of potential small molecule hits that may modulate the target protein and have a preferred ADMET profile.

In vitro

A target protein of interest can be tested in a 96 well plate with a selection of small molecules by leveraging high-throughput techniques to screen for binding [26]. The researcher can use these results to make a much stronger correlation to the MoA for an active ingredient

In vivo

Rather than just limiting the assay to the target protein, the researcher can put an entire insect or pathogen of interest in the multi-well plate and expose it to varying concentrations of the active ingredient while measuring the impact in a dose- and time-dependent manner. This will allow the researcher to evaluate the **efficacy** of an active ingredient.

Lead Optimization
& Formulation Development

—

Phase I & Phase II

Timing: 12-36 months

Summary

Lead optimization and formulation development aims to take the understanding of the physical and chemical properties of an active ingredient and develop a seed treatment, in furrow, or foliar spray system.

Lead Optimization helps answer key questions to improve the efficacy and safety of the active ingredient:

1. How is the active ingredient absorbed and how will it move in the species of interest?

2. How strongly does it bind to the target of interest and how quickly does it generate a response?

Formulation science requires analyzing and developing how an active ingredient can be used with other active ingredients and inert ingredients, provide consistent binding to the target, minimize the use of safety limiting ingredients, and have a path to being produced profitably at the scale needed.

Human and environmental safety studies are vital to ensuring that a formulated product has the desired impact on the target organism with minimal off-target effects.

At the end of formulation development, the product is the formulation and not just the active ingredient.

Opportunities & Common Pitfalls

Evolving regulatory requirements. Regulatory requirements on micro-plastics and other formulary ingredients are evergreen. Product developers must seek paths for their products to work with biodegradable and environmentally minded ingredients.

The mixture challenge. Novel active ingredients need to be tested in combination with other products that will be applied at the same time (tank-mixed or sequential) or using the same equipment.

Volumes of application. With the emergence of precision application, farmers are demanding formulations be built with application volumes at the forefront. This is paramount as spray systems move toward low, very low, and ultra-low volume formulations.

Initial COGS assessment. For the ingredient(s) included, it is important to calculate early on if they will all scale or if there are limits on material supply.

Cost Range & Trend

Costs can range between **$68-83M**

Increasing with the requirements for toxicology and environmental testing.

Once the number of active ingredients for the lead molecule have been identified in early screening, they need to be optimized for performance. **Lead Optimization** & **Formulation Science** seeks to achieve three product characteristics: **Efficacy, Safety, and Manufacturability.**

Lead Optimization

Efficacy becomes the word of choice, when considering how well a product will work on its target of interest. The point of pursuing efficacy is to get the maximum response with the minimum amount of active ingredient. This phase also is aimed at answering the question: "Does the active ingredient consistently do what it needs to do?" The research team already started answering this question in the discovery phase and can now further optimize the active ingredient performance. While many measurements are used to define the quantitative structure-activity relationship between a target and active ingredient, the metrics below are foundational to answer optimization questions.

How is it absorbed and how will it move in a species of interest?	**pKa –** Acid-based dissociation constant that defines the acidic strength of a molecule in a solvent. The lower the value the more acidic the molecule. If a molecule has limited solubility in water, researchers will often determine pKa values in other solvent mixtures such as water/dioxane in which the molecule may be more soluble.
	LogP – Partition coefficient provides indications on whether a substance will be absorbed by living organisms or be easily carried away and disseminated by water. It measures the ratio of the organic solubility to the water solubility [9] and is usually calculated with an HPLC or shake flask methodology.
	LogD – Distribution coefficient that is a pH-dependent version of LogP and used to measure lipophilicity.
How strongly does it bind to the target and how quickly does it generate response?	**EC50 –** Concentration of the active ingredient that produces 50% of the maximum response from the target. There is no hard and fast rule as to what concentration is good enough to continue lead optimization, but usually researchers will want to see activity of at least at 1µM or less to move forward, with optimum activity hopefully occurring more in the nanomolar range.
	IC50 – Similar to EC50, this measures the concentration of a given inhibitor where the binding to the molecular target reduced by 50%.
	LC50 – Same as the EC50 but the phenotype measured is death of an organism.

Dosing studies are meant to be conducted both *in vitro* and *in vivo*. These studies require sourcing biological material to test, and the readout results should be simple and direct measurements of efficacy. The results of these assays also serve as a control benchmark for future testing of the active ingredient and as a baseline for comparison in future formulation testing under specific delivery mechanics.

Generating *in vivo* and *in vitro* proof of concept is generally advisable prior to considering moving forward into formulation optimization. Basic protein binding assays *in vitro* are key for hit validation, but doing additional whole cell or whole species assays will better capture multi-variate factors of an organism. While it might seem complex, it is often simpler to set up a cell-based assay or whole species assay to get clear results demonstrating whether the product is efficacious against the weed, insect, or pathogen of interest. These results also can be used with genetic analysis to better understand if there are potential mutations that, if present in the target of interest, will minimize the efficacy or durability of a new hit molecule in the future.

Formulation Sciences

Perhaps the most complex and opaque piece of the crop protection small molecule discovery is formulation development. There are very few university programs with a specific emphasis in formulation chemistry. Instead, training in this field is approached as a multidisciplinary study that combines biochemistry, physical chemistry, organic chemistry, and molecular biology principles. There are many different types of formulations used in commercial agriculture, but here we will focus on seed treatment formulations and foliar spray formulations.

Seed Treatment & Foliar Formulations
The most common type of formulations in the market fall into one of the six categories [10] below.

Type of Formulation	Abbv.	Description	Examples
Suspension concentrates	**SC**	Water based solution that requires having a melting point higher than room temperature. Seed treatments are often a version of suspension concentrate that have supplemental additives for nutrition and adhesion to the seed.	Fluopyram, Imidacloprid
Emulsifiable concentrates	**EC**	Usually liquid in a dispersed oil phase in an aqueous solution, combines the active ingredient with aromatic solvents that have a lower cost of manufacturing and are easily polarized. Emulsion droplets aim to be between 0.1 and 1.0µm	Prothioconazole
Capsule Suspension	**CS**	The active ingredient is encapsulated in a small microcapsule made of a polymer shell and mixed with a suspending agent. There is movement away from polymer shells to more biodegradable solutions.	Acetochlor
Soluble Liquid	**SL**	Simple water-based solutions that are used where the active has a high solubility. SLs scale easily and make up a lot of the market today.	Glyphosate, Glufosinate
Water Dispersible Granules	**WG**	Conveniently packages a solid granule that when mixed in a tank will dissolve in water into a fine particle suspension. [11] Often requires a wetting agent to help with better dispersal.	Atrazine
Wettable Powders	**WP**	Dry formulation that is leveraged for active ingredients that have high melting points and water-insoluble solids. WPs are mixed with water and other inerts, diluents, and surfactants prior to spraying.	Cypermethrin

Choosing which type of formulation to pursue begins with consideration of the crop and geography, and then moves to considering the properties of the active ingredient. As an example, it is unlikely a water-soluble liquid formulation will work for a highly hydrophobic active ingredient unless other technologies are used to provide the ability to mix soluble and insoluble actives together.

In addition to the active ingredient, a formulation also includes other ingredients that each have their own function and safety profile. These are usually known as the inert or non-active ingredients. Do not let the name inert fool you – these ingredients each have their own impact in the formulation. The regulatory profile of these components is significant and can vary by geography. The global and regional acceptance of inert ingredients should be assessed early in the formulation development process as failure to do so could be problematic in later stages. Some of the main classes of inert formulation ingredients are summarized here:

Surfactants (i.e. wetting agents)	Constructed of both hydrophilic and hydrophobic parts to enable oil and water to mix. A wetting agent is a type of surfactant that reduces the surface tension between two substances. A surfactant can come with an electrical charge (anionic or cationic) or not.
Diluents	The main solution that the active ingredient is diluted into. In the case of an SL formulation, it would be water. In the case of an EC, it might be petroleum-based solvent.
Fillers	Bulking agents added to the formulation for mass.
Binders	Leveraged in WG and WP formulations to enable resistance to physical and chemical stresses to reduce dusting.
Dispersing Agents	Works into the diluent to ensure that the active ingredient does not amass together in the solution and stays evenly mixed and spread when applied.
Encapsulates	Polymers or biologically-derived encased technology that isolates the active ingredient from the water or oil based formulation.

Formulations combine active and inert ingredients to yield a safe, application-compatible, stable product. While unique in their physical and chemical properties, each inert ingredient either ensures that the active ingredient effectively reaches its target of interest or supports the formulation stability. **At the end of Phase II, the product of the RESEARCH phase changes from being the active ingredient to the entire formulation**, and **the efficacy and safety of the entire formulation will be submitted for review by regulating authorities.**

Safety

Crop protection small molecules and their formulations aim to have the desired impact on the target organism with little to no off-target effects. In cases where there is potential for exposure to derivatives or intermediates of the active or inert ingredients, these too will have to be studied.

Human and Animal Safety and risk assessments include evaluation of the product in numerous safety studies, such as: (1) toxicological studies to determine potential adverse effects on all major organs (liver, brain, thyroid, reproductive organs, nervous system, etc.); (2) carcinogenicity, mutagenicity, reproductive toxicity, and endocrine disruption studies; (3) absorption, distribution, metabolism, and excretion (ADME) pathway studies; and (4) determination of the maximum dose at which No Adverse Effects (NOAEL) are observed in test species. Please note that NOAEL is a U.S. federal standard and may not comply with individual U.S. state or foreign agency requirements. Requirements for each type of study should be reviewed at national, state, and local levels for the desired market on a country-by-country basis. For products that will be used on crops that serve as animal feed, such as maize for making silage, a risk assessment of livestock animals will be necessary. Additionally, the list of animals for safety testing has continued to evolve and can require additional testing and proof of safety across a broader species panel.

Environmental Safety requires experimental studies and modelling, which authorities evaluate during the product registration process. In regions with well-developed programs to regulate crop protection products, safety assessments are based on the specific regional or national safety standards. When looking to register a product for use in a country with less developed standards, a common approach is to meet the safety standards of relevant regulatory regions and countries and assess if the product can be safely used under local conditions and existing regulations.

Opportunities and Pitfalls with Formulation Sciences

Formulation science deals with multiple challenges from extending shelf-life stability to improving the dispersion and delivery of an active ingredient. The challenges below highlight some of the recent opportunities created by the emergence of both technology and new policies around the world.

1	**Evolving regulatory requirements**	New requirements for environmental safety can emerge based upon continuous policy changes. As an example, the EU has recently passed Commission Regulation (EU) 2023/2055 restricting synthetic polymer microparticles. This will lead to the need for alternatives to many of the microplastics used in capsule suspensions.
2	**Mixture Challenge**	The use of a single active ingredient repeatedly can lead to resistance developing in the target. Therefore, it is important to work on formulations that enable the use of multiple active ingredients with different modes of action in combination to decrease the development of resistance. Each active ingredient will have unique sensitivities to moisture, pH, or temperature and may interact synergistically or antagonistically with other active ingredients.

The use of encapsulation and oil dispersion are enabling more active ingredients to be safely used together, and this area of research continues to grow. For a startup developing a new active ingredient, it can be both costly and time consuming to make a mixed formulation for use with other active ingredients. Some products may be sold as stand-alone products, but for any product that will be used in combination with others the first step should be ensuring tank mix compatibility with a secondary focus on mixture products.

3 **Delivery & Low Volume Formulations**

Ground-based and precision drone applications of crop protection products in agriculture are enabling the use of even lower dosing requirements. This can lead to lower costs for the farmer and reduce the risk of off target environmental impacts. With the rise of precision application came some new terms that do not yet have a consistent market definition. While some definitions are being developed [12], [13], [14], [15], for simplicity's sake in this document we will use the following definitions:

Type	Volume Application Rate
Standard Formulation	= or >50 L/Hectare
Low-Volume Formulation (LV)	49-20 L/Hectare
Very-Low Volume Formulation (VLV)	20-10 L/Hectare
Ultra-Low Volume Formulation (ULV)	<10 L/Hectare

ULV formulations have led to the use of ingredients that remain fluid and spread to improve coverage or change bioavailability through localized concentration gradients to have inelastic efficacy and performance at lower application volumes. Additionally, the goal of these formulations is to achieve better stickiness to vegetation as well as lower drift risk.

4 **Conduct an initial COGS assessment**

Once the product, including all active and inert ingredients, is better understood it is important to calculate if it will scale or if there are limits on material supply. Ingredients that are dependent on rare supply may either have cost or supply chain limitations that prevent the formulation from becoming economically viable at scale. This assessment of a formulation's manufacturability is revisited frequently as the chemical synthesis and chemical process approaches are continuously improved (see next section).

Cost of Research

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From 1995 to 2019 the cost of hit discovery, lead optimization, and formulation development that occurs between Phase 0 and Phase II increased from $72M to $127m in large part due to the growing cost of chemistry discovery and biological screening [1]. Today, the use of in silico computational techniques has reduced the upstream cost associated with the discovery of lead compounds. Now, fewer compounds must be chemically synthesized for biological screening in vitro and in vivo to discover and optimize a new active ingredient (hit). Unfortunately, although virtual screening was used frequently in the 2000's and lead to significant reduction in costs for hit discovery, the savings have not yet been reflected in the reported costs for new product development.

Key Trend 1

A more efficient in silico program should lead to a smaller number of potential hits that require biological assays to screen for an efficacious compound. This should enable a faster path into Phase II Lead Optimization. While some discovery programs claim more dramatic numbers, one assumption is that at least 25% of the chemistry costs from the 2014-2019 surveyed costs of $64M have been mitigated down to $48M, resulting in a **$16M decrease**.

Key Trend 2

Early toxicology and environmental testing costs are expected to continue to rise as extra experiments, time, and resources are needed to meet the increasing safety testing requirements. Costs for safety testing grew from $7M to $11M between 2010 and 2019 (~50%). Using a consistent growth rate between 2019 and 2024 (5 years) would have had costs grow another 25% or a **$2.75M increase**.

$$Cost = [(Last\ Reported\ Cost) \pm Key\ Trends] * 10\ year\ inflation\ avg^{5\ years}$$

$$\$\mathbf{130}\boldsymbol{m} = [\$127m - \$16m + \$2.75m] * (1 + 2.73\%)^5$$
$$\text{(Hit Disc)}\quad \text{(Eco/Tox)}$$

[1], [16]

This report will refrain from providing an exact number but uses a 10% variance range to estimate that the **cost of Phase 0 – Phase II Research is between $118M and $143M.**

Phase III – Phase V: Development

Scale-up Production Chemistry

Phase III & Phase IV

Timing: 36-48 months

Summary

Scale-up production chemistry focuses on finding an economical, safe, and scalable chemical synthesis route that is process optimized for producing the active and any other key ingredients or their pre-cursors in a formulation.

Once a chemical synthesis route is found, companies must make the decision to either externally source, contract/toll manufacture, or internally build capacity to produce the final ingredient(s) for a formulated product. The production method decision hinges on a few key considerations including **economics**, **safety**, **logistics**, and **policy**.

Coming out of this area of research, a company should have a process chemistry pathway defined for the active ingredient, a pilot production facility built or made available, and production strategy for any key ingredients and any rate-limiting pre-cursors that is de-risked from global and commodity market considerations.

Opportunities & Common Pitfalls

Diversify the production supply of key raw materials, pre-cursors, reagents, and ingredients(s) protects from future supply risks.

Sourcing more sustainable starting materials without sacrificing on COGS.

Reaction byproducts and heat must be managed to minimize scale-up production risk and enable the recycling of energy and by-products.

Trust but verify. Staying on site for installations can help avoid issues and provide better collaborate with builders in case any issue or need to pivot arises.

Cost Range & Trend

Costs can range between **$31-38M**

Maintaining flat due to the ability to access pre-existing infrastructure while there is high susceptibility to the cost of raw materials.

This chapter will not specifically get into the science of **chemical synthesis** and **chemical process optimization** foundational for scaling up the production of a new product, but brief overviews are provided below:

Chemical synthesis refers to the culmination of all the reaction steps taken to get from a hit molecule to the final active ingredient. There can be a single or multiple chemical reactions needed to produce the final molecular product. Each one of these steps is a reaction that requires its own optimization. An overview of chemical reaction optimization can be found in the 2023 A Brief Introduction to chemical reaction optimization [17].

Chemical process optimization is the system engineering methodology used to improve the efficiency and profitability of a chemical process by implementing manufacturing procedures that improve the yield of desired product, minimize waste production, reduce energy consumption, and improve process safety. An overview of this can be found the 2022 editorial Integration and optimization in chemical process industry [18].

Whether the final product is internally manufactured or outsourced to a toll manufacturer, building or having access to a pilot facility can be critically informative for chemical process optimization. Pilot facilities allow for the continuous optimization of the synthetic and mechanistic processes involved in chemical synthesis. Pilot facilities enable quick process chemistry support and are key for early-stage synthesis of the product candidate for testing.

As the active ingredient moves through development, researchers often find that the initial chemical process is not the best option for larger-scale production. For example, the initial synthesis route might require expensive reagents, present challenging operating conditions, or create possible safety hazards when performed at larger volumes [19]. In addition, reaction times and complicated product isolations may lead to lowered capacity (throughput), higher equipment demands, and higher production costs. Stepwise evaluations of the chemical process allow for the collection of process data and a fundamental understanding of the opportunities for optimization. Building a pilot plant supports the planning and management of secondary reaction products, management of heat and carbon emissions, and informs understanding of the reaction chemistry efficiency at scale.

The decision on whether to build manufacturing capacity or access toll manufacturers includes considering economics, safety, logistics, and policy. Key questions are:

Economics	How can the product most cheaply be produced via the optimized chemical process, factoring in both capital facility and continuous operational costs?
Safety & Logistics	How can the product and any of its pre-cursors safely be made and reliably delivered to its destination with minimal risk to employees and the environment?
Policy	Is the chemistry production and manufacturing of the final product or any of its pre-cursors impacted by any regional, national, or international policy?

These considerations in combination will help inform the best path of production. As an example, a startup may consider toll manufacturing with an international contract manufacturing organization (CMO) who operates at a lower cost. However, when logistical shipping concerns, product stewardship, and international policy between the startup's country and the CMO location country are considered, the decision may change.

Opportunities and Pitfalls with Scale-up Production Chemistry

1	**Diversify production supply**	A startup may also consider minimizing its production supply risk by having multiple manufacturing relationships. Having a diversified supply chain decreases risks associated with the logistic and policy considerations mentioned previously. Examples have arisen where global trade has slowed down due to limitations on waterway throughput or weather pattern changes. Policy risk includes taxation, currency exchange, and stewardship as considerations that make the case to ensure supply from more than a single provider for any key ingredient, precursor, or intermediates.
2	**Sustainably sourcing starting materials**	The decision on where to source starting materials is an important consideration. If a CMO can produce most of your starting material at lower cost, it can be simpler and cheaper to source from them rather than build manufacturing capability. Supply chains are often spread across multiple manufacturing sites, so isolation of intermediates and shipping to other facilities for downstream reactions will require registration and tracking. Today, the full life-cycle-analysis of any product's carbon impact is a growing consideration, but working with multiple manufacturing sites to optimize cost and diversify risk to the product supply can possibly increase the carbon footprint when factoring in shipping between sites. Finding suppliers who sustainably produce starting materials, intermediates, or the final product while minimizing the distance they travel can lead to reduced emissions.
3	**Reaction by-products and heat must be managed**	Exothermic reactions that produce heat may not be an issue at lab or pilot scale but could become an issue when metric tons of material are being produced each day. Closed loop facilities that leverage their own exothermic reactions as energy for the endothermic reactions have a better carbon footprint. Likewise, many secondary products considered waste by some can be leveraged as inputs for creation of new additional products. As an example, methanol is a byproduct of many reactions and may be recovered for use as a solvent or reagent in another process. The recovery and use of byproducts are very common practices utilized by integrated chemical manufacturers to reduce costs and waste.
4	**Trust but Verify**	Too often when installations are contracted out the 3rd party company is trusted to do the appropriate installation. When thinking about the testing and scale for a startup, time is critical. Having the innovator's own process chemists and engineers on site to collaborate on all installations is critical to ensuring success. Failure to do so may lead to lack of oversight that can cost months of testing time. Even if an installation delay has not increased a company's construction costs due to insurance/guarantee of installer, the time lost can translate to a season of product for the agricultural market. Real-time analytics on the reaction process and composition also can lead to quicker optimization of the chemistry.

Scale-up production requires the expertise of chemists and engineers to come together to manufacture innovation at scale and drive down COGS of new products.

Field and Registration Trials

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Phase II, Phase III, Phase IV, and Phase V

Timing: 72-84 months

Summary

Conducting field and registration trials is the most expensive activity in bringing a new crop protection product to market. This makes it even more critical to ensure special attention is paid to experiment design, site selection, mixing products, and stewardship and regulatory requirements.

Experiment Design and **Site Selection** can minimize weather and random effects, allow for measurement of the null hypothesis, and ensure statistical power of field trial results. Testing partnerships serve as early market and business development to achieve belief among the future customer base.

Mixing products answer the question on whether a given crop protection product has a synergistic, antagonistic, or neutral effect when combined with other products that would be applied to the field at the same time.

Following the **regulatory requirements** set by the appropriate agencies and **stewardship best practices** will ensure that all testing, including residue and decline trials, are well executed and drive a quick and safe path towards product registration.

Coming out Phase IV the product should be fully registered and efficacy well defined. Phase V going forward will focus on broadening field testing and data generated to support market expansion opportunities.

Opportunities & Common Pitfalls

Engage farmers and support organizations. By engaging early, researchers can ensure support, advocacy, and 3rd party verification by market partners.

Missing Positive Controls. Failing to test early enough with the appropriate positive control(s) may mislead the researcher about the efficacy of the product. Crop protection should be testing potential new products in the full system of products that a farmer is using.

Underestimating Field Trial Costs. Contracted growers often expect a premium over commercial operations and generating additional data points may come at additional cost.

Cost Range & Trend

Costs can range between **$163-200M**

Increasing significantly due to the cost associated with conducting the necessary field trials to:

1) Meet and satisfy the regulating authorities.
2) Meet and satisfy the testing demands of customers and distribution partners.

Field trials are the costliest effort in most agricultural research pipelines. There are specific and strict requirements when it comes to registration trials, but most fields trials aim to answer the question: Does this solution safely work in the field with the current and future agronomic practices across a variety of geographies, soil, and weather conditions?

While the question seems simple enough, if you break it out into its components there are multiple questions that each require their own experimental design.

- Crop safety and environmental persistence studies across multiple environmental conditions
- Impact of performance of product by farm practice (tilling, irrigation, etc.)
- Impact on soil microbiome and nutrient composition
- Weather pattern correlation studies (days after rain)

Many of these studies can be combined for greater power analysis, however, others may not apply. Remember the more data collected on each trial provides better product understanding, with the tradeoff of higher cost of data collection. Researchers can opt to take soil samples at every field, however, to do so can increase the cost of a field trial based on labor/effort.

When looking at establishing a field trial testing program for a crop protection product, key areas to focus on are:

1 **Experimental Design**
2 **Site Selection**
3 **Mixing products**
4 **Stewardship or Regulatory requirements**

1 Experimental Design

Experimental design is critical to answer key questions about how a crop protection product will work in the field. The design of an experiment should include all the products of interest to be tested as well as proper control groups. This should include a basic untreated control and a positive control group. The number of plots included in an experiment, number of replications, and number of fields and locations where an experiment (trial) is run will determine whether a researcher can prove with statistical significance that their product works. In the registration section below are links to EPA, USDA, and FDA guidance on **registration trials** with specific requirements on this. When researching product efficacy, four of the most frequently used experimental designs are illustrated and summarized below.

Random Control Block (RCB)

RCB experimental design randomizes which plot gets what type of treatment (entry). If Entry 1 was low treatment, Entry 2 was medium, and Entry 3 was high treatment, then by randomizing where they appear in single replication of an experiment the researcher can overcome any field-specific bias. What kind of biases are being avoided? For example, picture all the Entry 3s are kept in the right most column of the example here. This column might be the closest to a road or river. Dust from the road or the potential flood of the river might impact the performance of that right most column of plots differently than the other columns. Were that to happen, all data on how Entry 3 performed in a field would be lost. In an RCB design with 4 replications (as visualized), the design

ensures that only one plot worth of data with regards to Entry 3 is lost. The use of border plots or other control factors can also mitigate environmental effects, but an RCB design allows for mitigation of both environmental effects and human selection bias.

Randomized Control Block

Control	Entry 2	Entry 3	Entry 1
Entry 2	Control	Entry 1	Entry 3
Entry 1	Entry 3	Control	Entry 2
Entry 3	Entry 1	Control	Entry 2

Replication 1
Replication 2
Replication 3
Replication 4

Group Block Design (GBD)

GBD is like RCB design except not every entry is randomized in the experimental replication, rather the entries are grouped by a shared attribute. In the example here, entries are grouped by which adjuvant was added to the formulation and within each group the entries are then randomized. Groupings can be of either equal or unequal sizes. It is important to remember the entries within a group remain together but are placed in random order within that group. The groupings then themselves should be randomly assigned.

Group Block Design

Entry 6	Entry 6	Entry 6	Entry 1	Entry 4
Entry 9	Entry 10	Entry 7	Entry 8	Entry 5
Entry 15	Entry 13	Entry 17	Entry 18	Entry 16
Entry 12	Entry 11	Entry 14	Entry 20	Entry 19

Group 1	Adjuvant 1
Group 2	Adjuvant 2
Group 3	No Adjuvant
Group 4	Adjuvant 3

Split Plot & Strip Plot

Split plot and strip plot trial types are variations on the GBD where within large plots two variables are tested simultaneously. Variable A would be tested in vertical strips and Variable B would be tested in horizontal strips. As an example, Variable A could be a crop protection small molecule product and Variable B the irrigation volume. This generates a gradient of performance and interaction effects for the researcher analyze.

Side-by-Side

Side-by-side trials are a variation on the GBD where multiple replications of a two-entry test are leveraged. These are usually conducted with large scale plots and are often a best-in-class methodology to test a late-stage product against the positive controls currently used in the market. Side-by-side replicated trials are often used in the development of marketing material and commercial sales numbers.

2 Site/Location Selection

The goal of fields trials should be to remove as many variables as possible, including weather, to best assess the direct impact of the product. Early in the product testing cycle field trials will be conducted at a smaller number of locations to test general efficacy, and then later in the product testing cycle a larger number of locations will be tested enveloping a wider range of environmental variables. When setting up field trials for crop protection, it is critical to accurately measure the presence of the pest of interest that the product is looking to address. Leveraging historical data and predictive tools, researchers can better select fields where there is likely to be sufficient pest pressure. When establishing trial design in these areas, the experimental design will allow more immediate comparisons to the performance of fields with and without the product, thus allowing for better testing of the **null hypothesis**. The null hypothesis is the comparison of the product to how a crop would perform in the absence of any treatment. In the case where there is pest pressure, the researcher would expect to see a negative impact from the pest on the plots with no treatment. However, if there is not sufficient pest pressure at the location, then the untreated acres may look exactly like the treated acres. This emphasizes the importance of location selection for pest pressure when setting up trials. Certain testing sites and locations can also be approved for inoculation studies, where the pest of interest is intentionally introduced to test products. These sites are highly regulated, and researcher will need to work closely with the appropriate agencies in these trials.

3 Mixing Products

If the basic control group will have no crop protection product applied and the positive control group will have modern best practices applied, then it is important to run a mixed product analysis. This will answer whether a crop protection product has a synergistic, antagonistic, or neutral effect with the other products applied to the field.

In the example of a new seed treatment for fungicidal control, seed treatments can be formulated and layered to minimize interaction between products on the seed. However, there is only so much that can be added to the seed before it affects the seed flow rate through a planter.

Also, as the coating of the seed breaks down, the layers of treatments may begin to interact with each other. If a new fungicidal seed treatment and biological seed treatment for seed germination are layered, the researcher will want to know how they interact. If the fungicide has a negative effect on the seed germination treatment, it is unlikely that these products will be stacked and one would have to be sacrificed or applied in a different manner.

In foliar applications, crop protection products are often tank mixed or sprayed at the same time. Testing which products can be tanked mixed is usually done during formulation testing, and this will continue in later stages as multiple products are spray applied in the field. It is important to analyze by crop and growing stage what the most frequently used products are and to establish trials that integrate the new product into current field-testing spray and irrigation practices.

4 Stewardship or Regulatory Requirements

Crop protection products are one of the most stringently regulated products in agriculture today. Before crop protection products can enter the market and be used by farmers, they undergo country-dependent evaluation and approval by local authorities for each targeted country to ensure that they may be used safely under local conditions [20]. If the product is entering the international commodity market, the product developer (or importer depending on the agreement) should seek not only product authorizations in the country where the product will be manufactured and sold but also import tolerances/authorizations for key import countries to follow accepted industry standards. The International FAO Code of Conduct for plant protection products and the regulatory standards of Organization for Economic Co-operation and Development (OECD) set minimum standards for testing. Import approvals require time and focus to work with the appropriate agencies. Scoping the scale of your product reach early on will allow for planning how to best engage regulating authorities globally.

In the U.S. as an example, crop protection products are regulated at the federal, state, county, and local levels. Compliance at the federal level includes[10]:

- **F**ederal **I**nsecticide, **F**ungicide, and **R**odenticide **A**ct (**FIFRA**) enforced by the EPA ensures that products do not cause unreasonable adverse effects on human health or the environment.
- The **F**ederal **F**ood, **D**rug, and **C**osmetic **A**ct (**FFDCA**) enforced by the Food & Drug Administration (FDA) requires the establishment of legal limits for pesticide residue in or on agricultural commodities.
- The **E**ndangered **S**pecies **A**ct (**ESA**) administered by the **F**ish and **W**ildlife **S**ervice (**FWS**) and National Marine Fisheries Service (**NMFS**) ensures that any action authorized by a federal agency will not likely jeopardize the continued existence of any listed species and is managed by services outside of the EPA.

In the United States, state pesticide laws govern the use of pesticides at state level. All federally approved pesticides must also be approved at the state level.

[10] There are also transportation, occupational, and advertising regulations to consider

When conducting R&D field trials, **stewardship is important**. Below are seven key principles[11] of stewardship that should be applied during crop protection small molecule product development.

1 Obtain country-specific important approvals and testing permits or authorizations for non-registered products.

2 Experiments/trials including the use of experimental products will be conducted by trained personnel who wear appropriate personal protective equipment (PPE) as determined by the human risk assessment.

3 Protocols and procedures are established when performing trials to prevent non-registered products from entering the food or feed chain.

4 Experimental products, seeds, and plant materials will be labeled clearly, meet applicable regulatory requirements and include information about safe handling.

5 Reasonable efforts will be made to ensure limits on potential cross contamination of any experimental product.

6 Crops and harvests from trials with non-registered products will be destroyed, unless otherwise allowed by regulations and laws.

7 **Residue trials for crop protection products will be conducted in accordance with national/regional regulatory requirements prior to marketing** such as in accordance with Codex Alimentarius and FAO guidelines.

Opportunities and Pitfalls with Field and Registration Trials

1	**Engage Farmers and support organizations**	Growers associations, farm bureaus, research farms, and land grant universities all help advance and bring the best possible products to market to improve farm productivity. Engaging early in the testing process of a new product with these organizations empowers them to provide their own resources to ensure successful trialing of new products and advocacy of the results generated. There are over 100 organizations in the U.S. alone dedicated to improving farm productivity and farmer access to resources.[12]
2	**Missing Positive Controls**	Too often, early-stage products are only tested against the null hypothesis, but it benefits researchers to ensure that proper positive controls are included in early-stage experiments. A common positive control is the current form of best practice for controlling

[11] Not an all-inclusive list

[12] The following Wikipedia page gives a guide to some of these organizations, however, please note that this list is NOT all inclusive.

Control	Control	Control	Control	Control	Control	Control	Control
Control	Entry 1	Entry 1	Entry 1	Entry 1	Entry 1	Entry 1	Control
Control	Entry 1	Entry 1	Entry 1	Entry 1	Entry 1	Entry 1	Control
Control	Control	Control	Control	Control	Control	Control	Control
Control	P.Control	P.Control	P.Control	P.Control	P.Control	P.Control	Control
Control	P.Control	P.Control	P.Control	P.Control	P.Control	P.Control	Control
Control	Control	Control	Control	Control	Control	Control	Control
Control	Entry 2	Entry 2	Entry 2	Entry 2	Entry 2	Entry 2	Control
Control	Entry 2	Entry 2	Entry 2	Entry 2	Entry 2	Entry 2	Control
Control	Control	Control	Control	Control	Control	Control	Control
Control	Entry 3	Entry 3	Entry 3	Entry 3	Entry 3	Entry 3	Control
Control	Entry 3	Entry 3	Entry 3	Entry 3	Entry 3	Entry 3	Control
Control	Control	Control	Control	Control	Control	Control	Control
Control	P.Control	P.Control	P.Control	P.Control	P.Control	P.Control	Control
Control	P.Control	P.Control	P.Control	P.Control	P.Control	P.Control	Control
Control	Control	Control	Control	Control	Control	Control	Control

Entry 1	Low volume
Entry 2	Mid volume
Entry 3	High volume
Control	No treatment
P.Control	Standard Practice

a pest of interest. This can be anything from an existing crop protection product to simply ensuring a crop rotation cycle to avoid persistence of a pest. For any new product to succeed in the market, it must demonstrate a significant performance and/or cost advantage over the existing practices and products in market. Therefore, it is critical to include a positive control in the experimental design. The example design below highlights how an experimental trial might be constructed for a given field.This design shows one replication of each volume formulation for the product being tested in a single replication experiment. In an actual field trial, a researcher will want to either have multiple replications in a field or multiple field trials at a given testing location to ensure that any environmental effects are mitigated. In the trial design above, if the field went through a minor flooding event and the top five rows were flooded, then the researcher would have no data on low volume formulation. Luckily, they would still have some data on the positive control. One of the goals of trial design is to mitigate these effects. Depending on the size of the plot and the accuracy with which a crop protection product can be sprayed, the researcher may choose to put control plots in between the testing rows.

3 Underestimating Field Trial Costs

The cost of contracting a grower to execute a field trial includes land rental, labor, planting, monitoring, measurements, data upload, reporting, and harvesting. There are several useful calculators for this:

University of Maryland Calculator
University of Illinois Crop Budget

A contract grower who is engaged to conduct a field trial will expect a guaranteed payment premium over what they would otherwise expect if they grew a commercial crop. For this reason, it is much more costly to run a single acre tomato field trial in California than it is to conduct the trial of one acre of corn in Illinois. A basic guidance for budget building purposes is to look at average yields in the area and budget a 10-25% premium payment for a field trial.

Cost of Development

—

From 1995 to 2019 the cost of conducting the needed scale-up production, field trials, and product registrations increased from $80M to $175M (including the cost of registration in both the EU and U.S.) [1].

Trend 1

Most of this growth in cost came from expansion of the requirements for field trial performance and proof of environmental safety. Since 2019 there has been continued expansion in the number and amount of testing and trialing needed for product registration in the EU and U.S. This is inclusive of the environmental and animal safety requirements, indicating a larger growth of cost for registration. Taking a modest 15% assumption in cost growth since 2019, this would only be about half the growth rate seen between 2010-2019 and would translate to **$6M in additional cost.**

Trend 2

Field trial results must be conducted not only in a statistically significant manner. Results also much be above reproach, and engaging with 3rd party farmers, non-profits, and large institutional ag organizations will help ensure that. This may require conducting extra field trials to prove efficacy and to gain the support of the broader retail and ag industry so that when the product is ready for market there are customers willing to adopt the product. Conducting partnership field trials can add an additional season or two to the development timeline before entering the market. Taking 7 years as the standard testing period, and using the 2014-2019 numbers, this would mean ~$8M/year in field testing costs. To account for the cost of an additional year's worth of testing with partners an **additional $8M in cost is added here.**

$$\$\mathbf{216}\boldsymbol{m} = [\underbrace{\$175m}_{\text{(Reg Trials)}} + \underbrace{\$6m}_{\text{(Field Test)}} + \$8m] * (1 + 2.73\%)^{7}$$

Over the next few years, the use of computational and statistical models will improve our field trial design, offsetting some of the increased cost, but if the trend of registration trial and environmental chemistry requirements continues as it has historically, costs are expected to increase in this category.

This leads to the estimated cost of Phase III – Phase V: Development to range from $194M-238M.

Summary for Crop Protection Small Molecules

Small molecule crop protection products can take a long time to bring to market and cost hundreds of millions of dollars to develop. However, they represent some of the most impactful agricultural products on the market today because of their specificity, scalable production, and ease of use.

Cost Summary	Estimated Time to Market
Research **$118 - $143m** **Development** **$194 - $238m**	**Research** **3 - 5 years** **Development** **7 - 8 years**
Total Cost **$312 - $381m**	**Total Time** **12+ years**

	Research $119 - $143 m ~ 3-5 years			**Development** $194 - $238m ~ 7-8 years		
	Phase 0	**Phase I**	**Phase II**	**Phase III**	**Phase IV**	**Phase V**
	Define the Problem	Pre-field Discovery	Early Product Development	Advanced Product Development	Pre-Launch Preparation	Launch & Market Expansion
Product	**Active Ingredient**			**Formulation**		
EFFICIACY						
Hit Finding & Screening Lab, GH	– Define crop & target - Map market size - Finish customer interviews	– Refine the target - In silico, in vitro, and in vivo testing - Identify lead compound(s)				– Use field results to screen for novel targets or compounds
Lead Optimization Lab, GH			– ADMET/Eco Tox screens run – Screen for efficiacy in GH			
Field Trials Field				– 10's of acres (in aggregate) – Prove efficiacy against null hypothesis and positive control groups – Implement partner engagement strategy	– 100' of acres (in aggregate) – Test in multiple soil types, weather, and agronomic practices – Test with industry partners – Tank mix analysis	– 1000' of acres (in aggregate) – Broaden field trials to new regions for potential market expansion
Scale-Up Production Chemistry Lab, Pilot, Manufacturing Site		– Check chemical synthesis scalability	– Conduct COGS assessment of initial formulation	– Establish scale-up chemistry process for active and inert ingredients – Access or build pilot production facility	– Build or contract manufacturing for active and inert ingredients and any precursors	– Continue to seek cheaper chemical synthesis and process options to drive down COGS
Formulation Lab			– Develop initial formulation – Finalize formulation "type" for product	– Refine the formulation for efficiacy and safety – "Lock-in" formulation to be submitted to regulators		– Continue to pursue formulations that further improve product performance
Safety, FTO, and IP Field, Specialized animal and environmental testing facilities		– Conduct IP review – Establish FTO and develop regulatory and IP strategy	– Begin to execute regulatory and IP strategy – Early regulatory testing for toxicology & environmental testing including residue and metabolism analysis	– Generate data for dossier(s) to regulators	– Provide supporting data for dossier(s) – Finalize go-to-market plan – Develop stewardship plan	– Continue to provide data regulating agencies

Crop Protection Small Molecule Opportunities & Pitfalls

Hit Finding & Screening	Lead Optimization & Formulation	Scale-up Production Chemistry	Field Testing & Registration Trials
In Silico ADMET screening **Overemphasizing virtual screening** **Production costs of any chemistry can become the limiting factor when manufacturing at scale** **Failure to conduct early IP review and develop an IP strategy**	**Monitor regulatory trends** on microplastics and other formulary ingredients for evergreen compliance **The mixture challenge** **Volumes of application.** This is paramount as spray systems move toward precision application and require low, very low, and ultra-low volume formulation	**Diversify the production supply** **Sourcing more sustainable starting materials** **Reaction byproducts and heat must be managed** **Trust but verify** with builders	**Engage famers and support organizations** **Missing Positive Controls** **Underestimating Field Trial Costs**

Product Pipeline Map (Detailed)

Research
(~$119-143M) Phase 0, Phase I, Phase II

Hit Finding and Screening
Phase 0, I

Facilities
Labs
Growth Chamber
Greenhouse

Cost Trend
Decreasing due to the use of artificial intelligence to better simulate molecular binding of small molecules to targets of interest, improved screening techniques

Target identification
- Genome-wide association studies (GWAS) or sequence analysis for target
- X-Ray Crystallography or CryoEM
- In vitro & vivo assay development

Compound Screening
- Structure-based or ligand-based molecule design and dynamics prediction for affinity and library screening against target
- Active ingredient synthesis
- In vitro and vivo assay testing

Lead Optimization & Formulation
Phase I, II

Facilities
Lab
Growth Chamber
Greenhouse
Small Plot & Field Trials
Specialized animal & environmental testing facilities

Cost Trend
Increasing due to growing toxicology and environmental testing requirements; however, these are partially offset by novel in lab testing methodologies

Molecular optimization for efficacy
- Pharmacokinetic and physical characterization of leading hits and MoA
- Design for stability, efficacy, and selectivity

Formulation development
- Formulation screening trials of A.I. with inactive ingredients (wetting agents, disintegrating, diluents, fillers, binders, etc.)
- Optimization of particle size, pH polymorphism, solubility, and viscosity

Early Regulatory: Toxicology & Environ. testing
- Mammalian acute and beginning sub-chronic
- Environmental and residue analysis
- Metabolism analysis and safety assessment

Development
(~$194-238M) Phase III, Phase IV, Phase V

Scale-up Production Chemistry
Phase III, IV, and V

Facilities
Lab
Manufacturing pilot facility

Cost Trend
Increasing due the cost of raw materials needed for facility buildouts or contracts for CMOs.

Formulation and A.I. Finalization
- Synthesis route optimization
- Formulation shelf-life stability and dispersion optimization
- Tank-mix analysis

Scale-up Manufacturing
- Pilot facility scale-up for synthesis of key active and key inactive ingredients
- Build or engage CMO for scale-up production to test the pilot

Field & Registration Trials
Phase III, IV, and V

Facilities
Lab
Field Trials
Specialized animal & environmental testing facilities

Cost Trend
Increasing due to the growing requirements for registration, efficacy, and environmental trials.

Wide-scale field trials
- Testing in combination with multiple soil types, weather conditions, and agronomic practices (e.g. irrigated vs. non-irrigated)
- Side-by-side against the market standard

Registration Tests & Field Trials
- Testing for plant, mammalian, and bird metabolism and toxicology
- Testing residue lifecycle in soil/water
- All other testing needed for regulatory approval

Glossary of Terms

Terms and definitions have been adapted from John Wiley & Sons Glossary of terms used in medicinal chemistry [21] for their applications in agriculture.

Active Ingredient	Molecule that provides direct biological activity or otherwise directly effects a target.
ADMET	Acronym referring to the absorption, distribution, metabolism, excretion, and toxicity profile or processes for a xenobiotic upon its administration in vivo. Note: ADME is also used to delineate these selected parameters within the context of a xenobiotic's chemokinetic profile.
AgTech	Short-hand term referring to Agricultural Technology; field of industry dedicated to the use of technology in agriculture with the goal of improving yield, efficiency, and profitability.
Allosteric	Site on a protein that can be bound by an effector molecule and is different from the protein's active site.
Assay	An investigative procedure or test to qualitatively and/or quantitatively measure the activity of research product.
Contract Manufacturing Organization (CMO)	Commercial organization that can be engaged to undertake specifically defined production of chemical or biological assets.
Contract Research Organization (CRO)	Commercial organization that can be engaged to undertake specifically defined studies.
Cost-of-goods sold (COGS)	All of the costs associated with manufacturing, delivery, and sale of a product.
Crop protection small molecule products	Made up of an active ingredient and other inert ingredients, formulated to be used as either seed treatments, in furrow, or as foliar applications to control pests and pathogens including weeds, insects, fungi, bacteria, and nematodes
Delivery	Process by which a crop protection formulation is administered to its intended target. Seed treatment, in furrow, and over-the-top foliar spray represent three delivery methods.
Experimental Design	How products are organized and tested in an experiment.
Field (In a Field Trial)	Made up of multiple plots in a usually contiguous piece of land.
Formulation	Mixture of active and inert ingredients that affects a target within an organism of interest. Herbicides, insecticides, fungicides, and nematicides represent a few formulations classes aimed at unique targets and organisms.
Freedom to operate (FTO)	In general, the ability to develop, make, and market products without legal liabilities to third parties. Relative to IP, FTO is the ability to develop, make, and market products without infringing the property rights of third parties.
Good laboratory practice (GLP)	Set of principles that provide a framework within which laboratory studies are planned, performed, monitored, recorded, reported, and archived. Note: These studies are undertaken to generate data by which the hazards and risks to users, consumers, and third parties, including the environment, can be assessed for researchers, agrochemicals, cosmetics, food additives, feed additives and contaminants, novel foods, biocides, detergents, etc. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments.

Good manufacturing practice (GMP)	Quality assurance process that ensures that agrochemical products are consistently produced and controlled to the standards appropriate to their intended use.
Hit	Molecule that produces reproducible activity above a defined threshold in an assay.
Inert ingredient (inert)	Any ingredient intentionally added into a formulation that is not the active ingredient.
In silico	A process performed virtually.
In vitro	A process performed outside of a living organism (e.g. test tube, culture dish, etc.)
In vivo	A process performed or taking place inside a living organism
Intellectual Property (IP)	Intangible property rights covering inventions (patents), commercial indicators (trademarks), creative works (copyrights), and secret information (trade secrets).
Lead Optimization	The synthetic modification of a biologically active compound to improve the stereoelectronic, physicochemical, pharmacokinetic, and toxicologic characteristics of a hit for agrochemical usefulness and safety.
Location (In a Field Trial)	Larger geographic area usually with consistent weather pattern. Can be made up of many Fields.
Mode of Action (MoA)	Describes the mechanism for the activity resulting from the application of an active ingredient.
Pest	An organism or virus that can negatively affect crop growth or yield such as a weed, insect, nematode, bacteria, or fungi.
Plot (In a Field Trial)	Small unit of land on which a distinct test will be conducted. Plots can have many Rows.
Potency	The dose of active ingredient required to produce a specific effect of given intensity as compared to a standard reference. Potency is a comparative rather than an absolute expression of activity. A compound's potency depends on both affinity and efficacy.
Protein	Large biomolecules and macromolecules that comprise one or more long chains of amino acid residues and are encode by mRNA.
Row (many plants)	A defined line of plants grown in a single line of a plot.
Target	The component of a biological pathway thought to be of key relevance in an agricultural plant, pest, or disease, usually taking the form of protein, DNA, or RNA.

Organizations

Environmental Protection Agency (EPA) enforces the national policies around product safety associated with Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)

United States Department of Agriculture (USDA)

U.S. Fish and Wildlife Service (FWS) enforces the national policies around product safety associated with the Endangered Species Act (ESA)

Organization for Economic Co-operation and Development (OECD)

National Marine Fisheries Service (NMFS) enforces the national policies around product safety associated with the Endangered Species Act (ESA)

Food and Agriculture Organization of the United Nations (FAO)

Food and Drug Agency (FDA) enforces the national policies around product safety associated with Federal Food, Drug, and Cosmetic Act (FFDCA)

United Soybean Board (USB)

National Corn Growers Association (NCGA)

Western Growers Association (WGA)

International Fresh Produce Association (IFPA)

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