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Issue Brief

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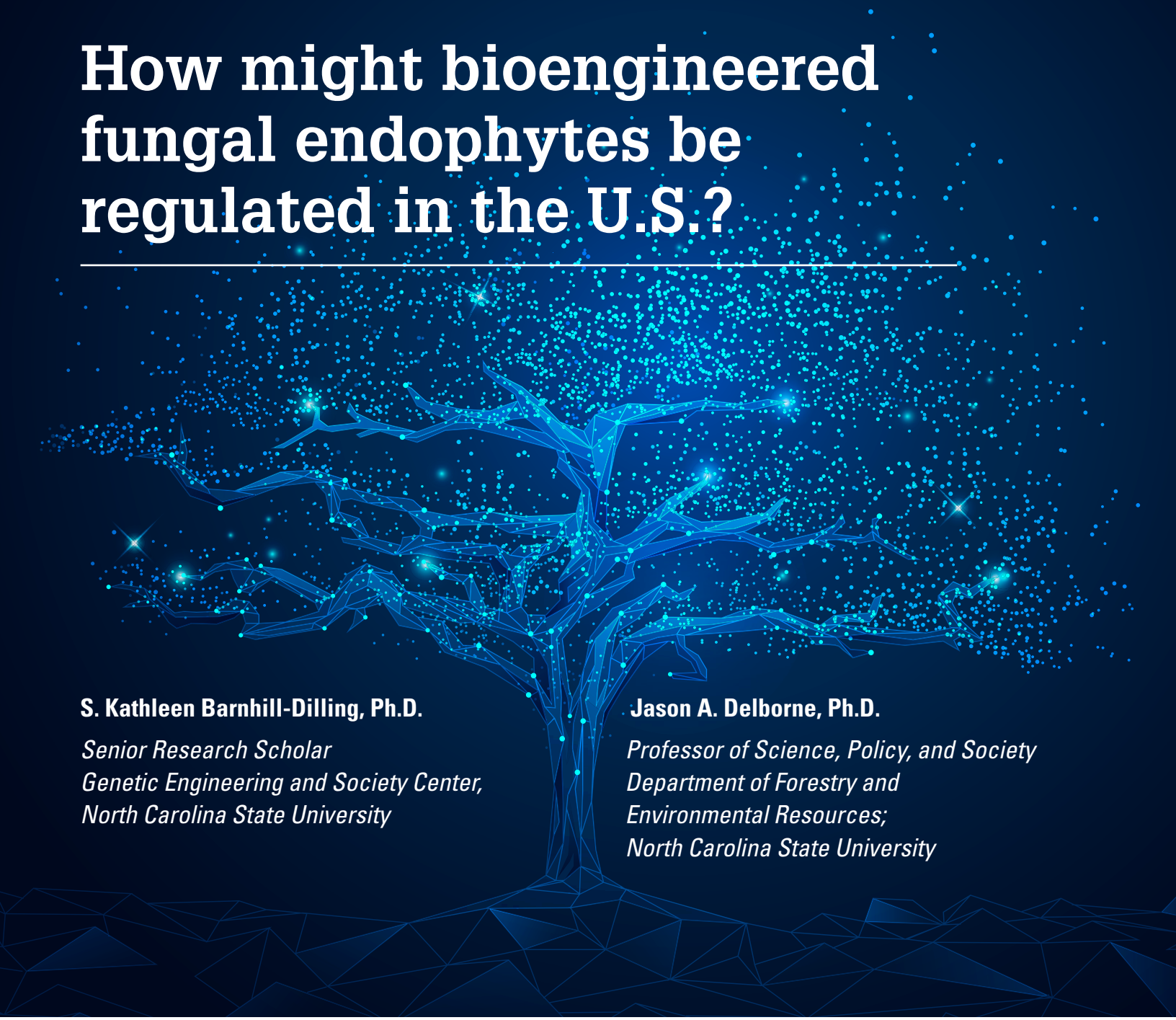

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HOW MIGHT BIOENGINEERED FUNGAL ENDOPHYTES BE REGULATED IN THE U.S.?

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I. INTRODUCTION

Scientists the world over are exploring new tools in order to find solutions for the sustainability and resilience of agricultural systems. For example, we are part of a team at NC State University that is conducting research about the potential development of genetically engineered or gene edited **foliar fungal endophytes (FFEs)** to be applied to agricultural crops. FFEs are microorganisms that live within plants' leaf tissue and often confer resistance to a variety of stressors such as pests or drought. This represents a departure from most of the existing agricultural biotechnology applications, which directly modify the plants in question, to modifying the microbiome that affects plant resiliency. While there is considerable enthusiasm for microbial solutions in agriculture, this relatively novel shift produces a number of technical, political, and social uncertainties about how our team's research might someday translate into useful technological products.

One of the key uncertainties about emerging applications of biotechnology rests in the regulatory and governance systems. Governance of gene edited FFEs is like a number of other new biotechnological applications: there is no perfect regulatory precedent, leaving a number of open questions. Moreover, the existing regulatory system, based on the Coordinated Framework for the Regulation of Biotechnology (hereafter, the Coordinated Framework) is dynamic. For example, as recently as April 2021, the **United States Department of Agriculture's Animal and Plant Health Inspection Service (APHIS)** SECURE rule **(Sustainable, Ecological, Consistent, Uniform, Responsible, Efficient)**, fundamentally reorienting its biotechnology oversight to the risks posed by the organism (Kuzma & Grieger 2020). Despite the potential for the Coordinated Framework to respond to new technologies, there is some concern that emerging technologies such as gene edited FFEs may fall into what some scholars call an "institutional void" as innovation may outpace guidance updates or that governance systems remain incomplete (Hajer 2003; Kuzma & Grieger 2020).

To address some of this uncertainty, this brief focuses on the policy implications of the development of genetically engineered or gene edited FFEs, outlining possible regulatory pathways to which these projects may be subject. We begin with an overview of the existing regulatory frameworks that govern biotechnology in the United States; such an outline highlights the different agency mandates that may trigger their oversight of modified FFEs. Secondly, we put forth hypothetical scenarios with various crop species, stressors, and FFE manipulation strategies, and link them to likely regulatory pathways. Using different scenarios will underscore how different transformation and end uses can result in different regulatory oversight. Finally, we will review some of the remaining uncertainties that will ultimately need to be addressed when scientists and developers have a product (or products) ready for deployment. These uncertainties underscore the dynamic nature of biotechnology governance in the United States.

II. THE COORDINATED FRAMEWORK FOR THE REGULATION OF BIOTECHNOLOGY

The Coordinated Framework is a document from the Office of Science and Technology Policy (part of the Executive Office of the President) that outlines a policy framework for regulating various products derived from biotechnology. First published in 1986, the Coordinated Framework has undergone a number of updates and revisions to respond to new issues as new innovations emerge, particularly with respect to gene diting techniques such as CRISPR, zinc finger nucleases, and TALEN methods.

Broadly speaking, the Coordinated Framework brings together key agencies to draw on their existing statutes to regulate biotechnology products based on verifiable scientific risk: the US Department Agriculture's Animal and Plant Health Inspection Service, the US Environmental Protection Agency, and the Food and Drug Administration. Each agency has its own mandate with respect to how a modified FFE might be governed depending on the type of organism, the nature of the transformation, and the intended uses of the product. In general, novel technologies such as modified FFEs are broadly governed by the principles of "science based" risk evaluations. In practice, this means that the agencies have a wide range of potential oversight activities: one event may require full risk assessments, while another an environmental assessment, and yet another may be subject to voluntary safety evaluations. In other words, there is a range of regulatory mechanisms that may prompt oversight of FFEs. Below, we review the oversight of each of the three primary agencies involved in the Coordinated Framework

US DEPARTMENT OF AGRICULTURE

Under the auspices of the **Plant Protection Act (PPA)** and the **Animal Health Protection Act (AHPA),** USDA's APHIS ensures that new biotechnology products — including fungi — are safe for both the environment and agriculture. In particular, the USDA — through its Plant Protection and Quarantine and Biotechnology Regulatory Service divisions — may have oversight of "importation, movement and field release of non-GE and GE microorganisms" (Wozniak et al. 2012, p. 62). However, as of April 2021, as per the new SECURE rule, regulatory oversight is **now based on the potential for plant-pest risk.**[1] The SECURE rule states that unless permitted, "no person shall move any GE organism that….

1 It is important to note that until recent changes brought under the SECURE rule, USDA would have been triggered by the use of certain plant pests such as *Agrobacterium tumefaciens*-mediated transformations or cauliflower mosaic virus as promoters. In other words, if a foliar fungal endophyte manipulation were to use one of these plant pests as part of the transformation process, USDA would likely have regulatory oversight under the Plant Protection Act and the National Environmental Policy Act

meets the definition of a plant pest… or is a microrganism used to control plant pests…" (USDA 2021). As part of moving through this refined regulatory process, the following dimensions will impact a modified FFE's regulatory pathway.

First, new products may actually be exempt from regulatory review. Two of the factors that determine exemption include (1) does the product include plant-trait-mechanism of action that has already been approved? Or (2) is the FFE product conceivably achievable through conventional breeding? If so, the modified FFE may be exempt from regulatory review.

However, we anticipate that given their relative novelty (as microbes that live systemically in crops), that the USDA will not consider FFEs exempt initially, in which case, the product will undergo a regulatory status review (RSR), beginning with plant-pest screening. Full details about the new review process can be found detailed in the SECURE rule language.[2]

US ENVIRONMENTAL PROTECTION AGENCY

Most of the regulatory conversations around manipulating the microbiome have centered around the role of the US Environmental Protection Agency. Authorized by the **Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)**, the **Toxic Substances Control Act (TSCA)**, and the **Federal Food, Drug, and Cosmetic Act (FFDCA)**, the EPA regulates any pesticide or protein or trait that has pesticidal properties under FIFRA, as well as genetically engineered microbes under TSCA. This regulatory authority extends to both human and animal consumption, as well as environmental effects on non-target organisms. The two policies most relevant to the fungal endophyte project are FIFRA and TSCA.

The **Federal Insecticide, Fungicide, and Rodenticide Act (**FIFRA) enables EPA to have regulatory oversight over microorganisms that may be used as a pesticidal product (hereafter **MPCAs, microbial pest control agents**), *whether or not those microorganisms are genetically modified*. Additionally, the intended purpose of the FFE and claims made to its use may also bring the FFE product under FIFRA oversight. MPCAs, which of course would include some applications of modified foliar fungal endophytes, may be subject to a risk assessment that includes product analysis (including identity and composition), evaluation of impacts on human health (including toxicity, infectivity, and pathogenicity), potential adverse effects on non-target organisms, and environmental fate studies (which for biotechnology notifications and some 'exotic' MPCAs, includes persistence in the environment and associated effects).

For any genetically modified microorganism that is intended to be used as a pesticide, including some of the potential applications of modified FFEs, developers must provide the risk assessor:

- the nature of the transformation event, including DNA sequences of transgenes,
- associated vector sequences with restriction map,
- DNA source information,
- an indication of transgene stability over multiple generations or growth cycles, and
- Confidential Statement of Formula: active and inert ingredients, concentrations of the microorganism (Wozniak et al 2012).

2 Note that the new SECURE rule went into effect for corn, soy, cotton, potato, tomato, and alfalfa on April 5, 2021 and will go into effect for all GE plants on October 1, 2021. Therefore we anticipate that the new rules for GE microorganisms will also begin in October 2021.

Under FIFRA, the EPA must also review and approve test plots for genetically engineered MPCAs through the Biotechnology Notification Process. As part of the review of a Biotechnology Notification application, EPA will determine if an Experimental Use Permit will be needed. Biotechnology Notifications are limited to 10 acres of terrestrial area (1 acre aquatic) for field testing. Further, the EPA must be notified about field testing; the EPA may issue an experimental use permit to allow for data collection that would be foundational for a meaningful risk assessment and an ultimate FIFRA Section 3 registration of pesticides. During the testing process, plants and materials that have been treated with the MCPA are prohibited from entering the food and feed supply with further oversight. MPCAs are granted temporary food tolerances under the Food Drug and Cosmetic Act as part of a FIFRA Section 5 Experimental Use Permit if they are applied to food or feed crops or produce derived from these crops.

The **Toxic Substances Control Act** (TSCA) oversees commercial, industrial, and consumer applications of microorganisms considered to be 'new' or intergeneric microorganisms, defined as those "formed by the deliberate combination of genetic material from organisms classified in different taxonomic genera, including microorganisms constructed with synthetic genes that are not identical to DNA that would be derived from the same genus as the recipient" (OSTP 2017). Microorganisms constructed with synthetic genes are also part of the TSCA purview. Important to note here is that TSCA is considered to be a "gap-filling statute for biotechnology products not regulated under other statutes" (Wozniak et al. 2012, p. 77). In other words, with the relative novelty of modified FFEs, the EPA's TSCA may well play the gap-filling role with respect to regulatory oversight. And within TSCA, there are two routes for approval of microorganisms: if the intergeneric microorganism is intended for commercialized uses, developers submit a **Microbial Commercial Activity Notice (MCAN)**; if the intergeneric microorganism will be introduced into the environment, developers must submit a TSCA Experimental Release Application. Additional information about EPA's pre-manufacturing provisions and reporting requirements are outlined in a guidance document entitled, "Points to Consider in the Preparation of TSCA Biotechnology Submissions for Microorganisms."

FOOD & DRUG ADMINISTRATION

As per the **Federal Food, Drug, and Cosmetic Act** (FFDCA), the **Center for Food Safety and Applied Nutrition (CFSAN)** applies the same rules to biotechnology derived products as it does all food and feed in the marketplace. As such, biotechnology derived foods are evaluated based on their safety and nutrition rather than the process that produces them. However, the FDA does review genetically engineered microorganisms that impact food safety or nutritional characteristics. The FDA's review process determines whether biotechnology derived foods are "substantially equivalent" to other foods in the marketplace. This review process is entirely voluntary, but it is believed that all biotechnology derived foods on the market have submitted their product to FDA for evaluation. While there are genetically engineered microorganisms on the market, it is unclear if genetically engineered or gene edited FFEs are similar enough to other products to be considered substantially equivalent. It is therefore likely that consultations with the FDA will be recommended.

III. HYPOTHETICAL SCENARIOS & REGULATORY PATHWAYS

In order to illustrate potential regulatory pathways for modified FFEs, we have developed four simple — and fully hypothetical — scenarios that were inspired by current efforts in the FUN-CROPS project. Each scenario highlights different dimensions of potential products that may trigger different regulatory oversight.

Scenario A. *Intra*generic gene edited endophyte comparable to events previously cleared by USDA, to be applied to soybean as an inoculant to confer drought tolerance (e.g., delay wilting by 2 weeks through reduction of water loss). Soybean may be used as food or feed.

Scenario B. *Inter*generic gene edited endophyte to be used as inoculate to enhance pathogen antagonism to Fusarium head blight (*Fusarium graminearum*) in wheat, which may be used as food or feed.

Scenario C. Genetically engineered endophyte that used *Agrobacterium tumefaciens* mediated transformation, developed to apply on the biofuels crop switchgrass for increased heat tolerance.

Scenario D. Genetically engineered endophyte that may be considered a plant pest to a non-agricultural plant, developed to apply to corn to prevent infection from southern leaf blight (*Bipolaris maydis*).

As Figure 1 suggests, there are a number of mechanisms that will trigger regulatory oversight, including the potential for the transformed endophyte to be a plant pest, to contain pesticidal properties, or demonstrate some other new characteristic. Modified FFEs will likely fall under the jurisdiction of USDA and/or the EPA depending on their transformation processes, characteristics of organisms, goals, and source DNA. Moreover, even in the absence of genetic transformation, the EPA would have regulatory oversight under FIFRA based on the intent or purposes of their use. Finally, the end uses will also impact regulatory oversight. If the FFE will ultimately impact the food or feed supply, then consultation with the FDA will also be recommended under the FFDCA.

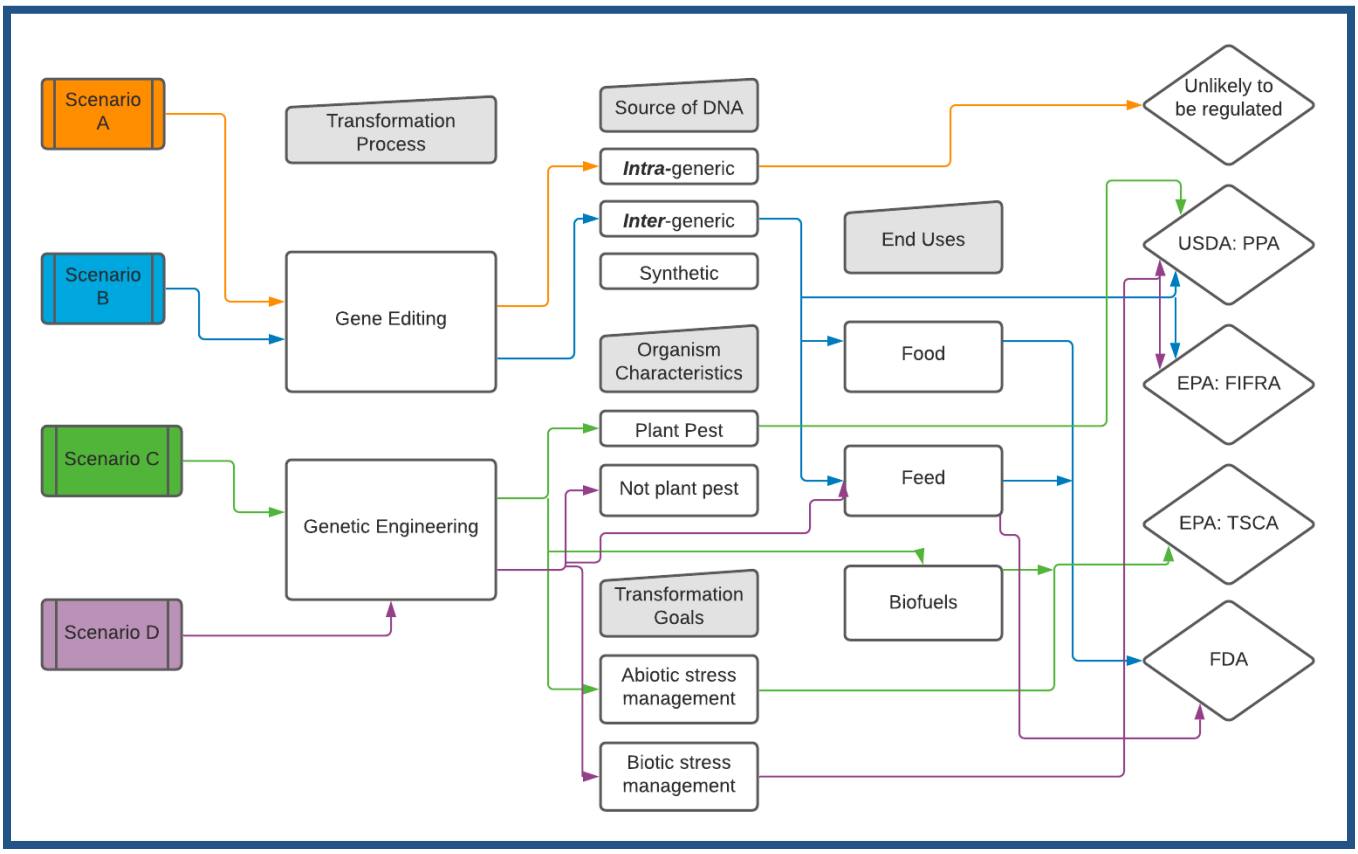

Figure 1. Potential Regulatory Pathways: Transformed Fungal Endophytes

IV. REMAINING UNCERTAINTIES

Policy-specific uncertainties remain about the potential regulation of gene edited or genetically engineered FFEs that may be relevant when developers are ready to bring products from the bench to the market.

GE Foliar Fungal Endophytes would be relatively novel biotechnology tools. The relative novelty of gene edited or genetically engineered endophytes may well trigger more comprehensive evaluations than plant crops elicit. While there are procedures in place to support the developer, some of the procedural requirements are data-intensive and laborious and specific requirements cannot easily be predicted at this stage of research and development.

Uncertainty surrounds the potential weediness or pathogenicity potential resulting from modifying the microbiome. While the benefits for harnessing the microbiome are well articulated (Mueller & Sacks 2015; Kaur 2020; Qui et al. 2019), there are also potential risks that some experts argue have been underestimated (Hart et al. 2017; Jack et al. 2020). For example, some scholars argue that microbial inoculants have the potential to become invasive. Moreover, "many endophytic fungi are closely related to pathogens and may transition from mutualists to necrotrophic pathogens, particularly under changes to the host environment" (Jack et al. 2020 p.3). Given anthropogenic climate change is predicted to alter myriad agricultural systems, this is particularly important. As a response, Jack and others suggest that modified microbes be engineered for "high host fidelity" in an attempt to avoid

unintended consequences. However, still other scholars firmly disagree with the potential invasive potential of microbes, essentially arguing that microorganisms respond to environmental conditions, rather than creating environmental conditions. This discrepancy in expert opinion exposes further uncertainty with respect to novel microbial product development, and this uncertainty may bear out in the risk assessment processes for modified FFEs.

Biotechnology policy in the United States is dynamic. As recently as April 2021, USDA began implementing new regulations for genetically modified organisms under the new SECURE rule; this "marks the first comprehensive reform of U.S genetically modified (GM) crop oversight" since the Coordinated Framework was established (Kuzma & Grieger 2020). While these changes may result in oversight exemptions of upwards of 99% of GM plants, the rule changes on microbial organisms may be less clear. Additionally, because the Coordinated Framework simply 'coordinates' existing agency and statutory authority, some policy and public administration experts argue that the regulatory landscape is patchy, inconsistent, and may be subject to interpretation. One modified FFE may be subject to oversight by all three agencies whereas another may be outside the purview of any regulatory oversight, but subject to voluntary evaluation (see Figure 1). The patchwork nature of existing regulatory oversight can make navigating product development challenging without specific guidance from regulatory experts.

Even if and when regulatory pathways are confirmed, there remain uncertainties about potential technology adoption. Preliminary research suggests that growers may be skeptical of microbial products because of past unkept promises, for example (personal communication). Additionally, consumer acceptance of novel biotechnologies may remain an open question (Hanlon & Sewalt 2020; Jones et al 2019).

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FUN-CROPS

Research scientists at North Carolina State University are exploring ways to harness plant fungal symbionts – specifically foliar fungal endophytes – to improve crop resistance to stressors such as drought, pests, and pathogens. Although this project is in an exploratory, basic research phase, the investigators recognized the importance of engaging stakeholders about their perspectives on the potential utility of fungal manipulations on crops.

For additional information about the project — including other project objectives and personnel — see https://hawkeslab.wordpress.ncsu.edu/funcrops/ or the CALS press release.

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GENETIC ENGINEERING AND SOCIETY CENTER

The GES Center at NC State University serves as an international hub of interdisciplinary research, engaged scholarship and inclusive dialogues surrounding opportunities, and challenges associated with genetic engineering and society. Positioned at the nexus of science and technology, the social sciences and humanities, the GES Center has taken a national and international lead in examining the technical, ethical, and societal dimensions of the products and impacts of biotechnology.

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