SYNTHETIC BIOLOGY AND THE U.S. BIOTECHNOLOGY REGULATORY SYSTEM:

Challenges and Options

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This project was funded by the Department of Energy's Office of Biological and Environmental Research, grant number DE-SC0004872: *Managing the Risks of Synthetic Biology: Assessing the U.S. Regulatory System*. Additional support was provided by the Alfred P. Sloan Foundation.

May 2014

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Executive Summary

In recent years, a range of new genetic engineering techniques referred to as "synthetic biology" has significantly expanded the tool kit available to scientists and engineers, providing them with far greater capabilities to engineer organisms than previous techniques allowed. The field of synthetic biology includes the relatively new ability to synthesize long pieces of DNA from chemicals, as well as improved methods for genetic manipulation and design of genetic pathways to achieve more precise control of biological systems. These advances will help usher in a new generation of genetically engineered microbes, plants, and animals that will, for the most part, be subject to a regulatory system that has been itself evolving for more than twenty-five years.

In the 1980s, the commercialization of microbes and plants developed using recombinant DNA technology led to the adoption of a U.S. federal policy that applied then-existing laws to these products. Under those laws, the three agencies with principal regulatory responsibility for these products – the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS), the U.S. Environmental Protection Agency (EPA), and the U.S. Food and Drug Administration (FDA) – have reviewed many products made using genetic engineering, including genetically engineered microbes, plants, and animals, for potential environmental, health, and safety concerns. The agencies have also issued regulations and industry guidance regarding genetically engineered organisms to respond to changes in technology and advances in scientific knowledge.

This study addresses how well the current U.S. regulatory system for genetically engineered products is equipped to handle the near-term introduction of organisms engineered using synthetic biology. While the current regulatory system has generated debate from its inception, here we focus on whether the advent of synthetic biology will raise new issues for the regulation of these products. In particular, we focused on those engineered organisms (for example, bioenergy crops and biofuel-producing algae) intended to be used or grown directly in the environment, outside a contained facility.

Our research concludes that the U.S. regulatory agencies have adequate legal authority to address most, but not all, potential environmental, health and safety concerns posed by anticipated near-term microbes, plants, and animals engineered using synthetic biology. Such near-term products are likely to represent incremental changes rather than a marked departure from previous genetically engineered organisms.

However, we have identified two key challenges to the current U.S. regulatory system posed by the introduction of organisms engineered using synthetic biology into the environment. For these challenges, we do not make specific policy recommendations, but rather set out options, including an analysis of the advantages and disadvantages of each option from a variety of perspectives for policy makers to consider. Policy responses will depend on the trade-offs chosen among competing considerations.

The key challenges and options to address them are:

Genetically engineered organisms are increasingly being developed in ways that leave them outside of APHIS' authority to review, and synthetic biology will accelerate this trend. Currently, APHIS' oversight depends on whether plant pests or some component of a plant pest is used to engineer the plant. These regulations covered almost all plants made using older genetic engineering techniques, but will not apply to plants engineered using several of the newer techniques. This shift will leave many engineered plants without any regulatory review prior to their cultivation in the environment for field trials or commercial production.

- Option 1: Maintain existing regulatory system and rely on a voluntary approach for those genetically engineered plants not subject to review. APHIS could maintain a voluntary system similar to their current regulatory procedures or product developers could use industry-developed standards to ensure that environmental risks are assessed and addressed.
- Option 2: Identify the most likely risks from newer generations of plant biotechnology and apply existing laws best able to mitigate them. One approach may be to use APHIS' authorities over noxious weeds to regulate biotechnology products. In 2008, APHIS issued a proposed rule for genetically engineered plants that incorporated both noxious weed and plant pest authorities, but even

after extensive public comment and stakeholder input, the rule has not advanced.

- Option 3: Give APHIS additional authority to review and regulate genetically engineered plants. This option would require Congressional action, which might be difficult to achieve.
- Option 4: Promulgate rules under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) or the Toxic Substances Control Act (TSCA) for EPA to regulate engineered plants. Both of these laws are broad enough to apply to genetically engineered plants, but such rules would be a major departure from the current regulatory system.

Synthetic biology will lead to an influx of genetically engineered microbes intended for commercial use, which may overwhelm EPA's Biotechnology Program. While EPA regulators have successfully reviewed such engineered microbes to date, this influx will include a larger number and more diverse set of microbes than the program has seen previously, including many with intended or possible environmental exposure. Moreover, as engineered microbes become increasingly complex, risk assessments will pose a greater challenge. EPA will require additional funding to meet the increased workload and expertise requirements. In addition, the agency may be constrained by the authority given to it under TSCA, which has been criticized as inadequate, both in the context of engineered microbes and more broadly. These issues could lead to regulatory delays for microbial products, inadequate review, and/or legal challenges.

- Option 1: If and when needed, provide additional funding for EPA's Biotechnology Program under TSCA and pursue efficiency measures to expedite reviews. Efficiency measures could include broadening exemptions for low-risk microbes and developing procedures to review environmental testing of engineered microbes on a programmatic basis (i.e. for multiple, similar microbes in a single submission).
- Option 2: Amend TSCA to strengthen EPA's ability to regulate engineered microbes. This option would require Congressional action and could either address engineered microbes specifically or could strengthen TSCA for all chemicals subject to the law.

In addition to these major challenges, we have identified three additional issues in the regulation of new engineered microbes that should be periodically revisited as the technology advances, but in our view, do not require action today. These issues include the regulatory treatment of two classes of microbes that are exempted or excluded from review by EPA and EPA's somewhat limited definition of "intergeneric microorganism."

In developing this report, we consulted with a wide range of experts to ensure a broad representation of knowledge and viewpoints, including U.S. federal agency regulators, legal and science policy experts, representatives from the biotechnology industry, and non-governmental organizations. This cross-section of views informed this report, but this study does not represent a consensus: the findings and conclusions here are ours alone.

Chapter 1: Introduction

1.1 Focus of the Sudy

Our purpose was not to revisit past issues, but instead to identify any new challenges that may arise for the regulatory system with the advent of synthetic biology.

We undertook this study to better understand how well the U.S. regulatory system for genetically engineered products will address organisms engineered using a set of emerging advanced genetic engineering techniques that, collectively, we call synthetic biology. We focus on those engineered microbes, plants, and animals that are intended to be used or grown directly in the environment, outside of a contained facility. This emphasis reflects the fact that many of the anticipated commercial applications using synthetic biology techniques currently under development, such as biofuel producing algae and bioenergy crops, are intended for use in the environment. In addition to potential benefits, these genetically engineered organisms can pose potential environmental risks. Regulation therefore plays a central role in maximizing the benefits and minimizing the risks of these new products.

Since the initial description of recombinant DNA technology in the mid-1970s, there has been a long and robust debate about the appropriate regulatory policy for genetically engineered organisms.[1] For this study, our purpose was not to revisit past issues, but instead to identify any *new* challenges that may arise for the regulatory system with the advent of synthetic biology, and if found, to present viable options that policy makers could pursue to address those challenges.

Throughout the report, we refer to organisms or products "engineered using synthetic biology" to distinguish them from the more inclusive category of "genetically engineered" organisms or products. "Genetically engineered" refers both to products engineered using synthetic biology as well as those engineered using older techniques. In this report, we use both of these terms to refer to the living organisms themselves and not to the non-living products (e.g., chemicals, biofuels, pharmaceuticals) that such organisms may be used to produce. Those secondary products may also be subject to regulation, but the focus of this report is on regulation of the organisms themselves.

The first phase of this study sought to determine whether products (i.e. organisms) engineered using synthetic biology would be treated by the U.S. regulatory system in the same manner as products engineered using older genetic engineering techniques. This analysis required a review of the wide range of U.S. laws and regulations that are used to regulate genetically engineered products. The regulatory system is a mosaic of many laws, each of which has a different focus and regulatory approach. Some laws require products to be approved by a regulatory agency before they can be marketed, including such products as pesticides, food additives, and human and animal drugs. Most products, however, are not required to obtain a pre-market approval but are instead subject to other laws that allow regulatory agencies to take action after a product is on the market if there is evidence it is causing harm. Many laws are focused on specific products (e.g. cosmetics, dietary supplements),

1 Policy debate about the role of regulation of genetically engineered organisms has a long history, going back to the Asilomar Conference in 1975, the U.S. Coordinated Framework for the Regulation of Biotechnology in 1986 (discussed in Chapter 2), and continuing to today's discussions and debates surrounding labeling of foods derived from genetically engineered crops. Over time, many studies reflecting a variety of perspectives have been written on the strengths and weaknesses of the U.S. biotechnology regulatory system, both in its approach and in its implementation (NRC, 1989; NRC, 2000; Chassy, et al., 2001; McGarity, 2002; Mellon & Rissler, 2003; PIFB, 2004; Miller & Conko, 2005).

or specific subsets of products (e.g. "new" chemical substances). We undertook a careful analysis of how U.S. federal agencies have used these laws to review the potential health, safety, and environmental concerns posed by genetically engineered products—in particular, those used outside contained manufacturing facilities—and consideration of whether those laws and associated regulations would apply in similar ways to microbes, plants, and animals engineered using synthetic biology.

In addition to comparing the regulatory treatment of products engineered using synthetic biology to products engineered using older genetic engineering techniques, the study also considered areas in which synthetic biology may create new regulatory challenges in other ways. In particular, synthetic biology has the potential to enable more powerful methods for engineering novel organisms cheaply and easily by a broader range of scientists. A rapid increase in the number, diversity and complexity of genetically engineered microbes, for example, could require an increase in EPA resources to maintain an adequate regulatory review process, as discussed in Chapter 4.

Because the focus of this study is on new challenges created by synthetic biology, this report does not detail ongoing controversies about regulation of genetically engineered organisms that are not foreseeably impacted by the newer methods of synthetic biology. However, when presenting the challenges and options we have identified, we are cognizant of the types of issues that have arisen in the past, including the perspectives and perceptions of stakeholders with different views. Throughout the study, multiple perspectives were included in order to best understand how the regulatory system is likely to be impacted by newer technologies and the pros and cons of the policy options.

Importantly, we do not attempt to characterize the risks created by any individual new product of synthetic biology. (For a discussion of hazard, risk assessment, and risk management, see Box A.) Any potential health, safety and/or environmental risks posed by a genetically engineered product will be specific to that product. Studies by the National Research Council (NRC) have repeatedly concluded that genetic engineering itself does not create unique hazards compared to other methods of genetic modification (e.g., traditional breeding or hybridization) (NRC, 1987; NRC, 1989; NRC, 2000; NRC, 2002; IOM & NRC, 2004). While these NRC studies did not separately examine synthetic biology as a specific genetic engineering technique, their reasoning applies equally well. Synthetic biology itself does not pose a hazard. However, some individual products engineered using synthetic biology could pose risks due to the nature of the particular genetic changes or constructs that are made, but those risks can only be assessed on a case-by-case basis. As noted below, the U.S. regulatory system reflects this principle that regulation should be based on the risks posed by a particular product and not on the basis of the process by which the product is made.

Any potential health, safety and/or environmental risks posed by a genetically engineered product will be specific to that product.

1.2 Synthetic Biology

"Synthetic biology" refers to a set of techniques that together provide scientists and engineers with far greater capabilities to engineer organisms than previous techniques allowed. The field includes the relatively new ability to synthesize long pieces of DNA from chemicals, as well as improved methods for genetic manipulation and design of genetic pathways to achieve more precise control of biological systems. (For more definitions of synthetic biology, see Box B.) The underlying principles for synthetic biology are the same as

Box A: Hazard, Risk Assessment, and Risk Management

One set of concerns about genetic engineering and synthetic biology focuses on potential risks to health, safety and/or the environment. For example, a health risk could arise if an engineered bacterium or virus inadvertently becomes more pathogenic, creating a risk for laboratory workers and, if the organism were to escape containment, the surrounding community (Berg, et al., 1974; NIH, 2012).

The concern has also been raised that a genetically engineered organism (microbe, plant, or animal) could have adverse environmental effects if released into the environment intentionally or inadvertently. Possibilities include harming desirable microbes, insects, plants, and/or animals, either directly (like a pesticide) or indirectly, by altering or occupying natural habitats (like an invasive plant). Concerns have also been raised that transgenes could flow into wild relatives, potentially affecting the fitness of those relatives or leading to the loss of desirable genetic diversity. There is also a concern about potential safety of the food or animal feed derived from genetically engineered plants. Because these organisms are living, with the potential capability to replicate and spread, there is the additional concern that mitigation measures may not be effective if there are unexpected adverse impacts (NRC, 2004; Snow, et al., 2005).

While people commonly refer to such concerns as potential "risks," more accurately they are potential "hazards." Hazards are the possible harmful outcomes; risk is the probability that such harmful outcomes might occur given that exposure has occurred (NRC, 1983). Risk is a function of the hazard, including its severity, as well as the potential for exposure, that would be required to result in the harmful outcome.

Researchers, developers, and regulatory agencies try to characterize risk through a process called risk assessment (NRC, 1983; NRC, 2009). To characterize future risks, for example, a risk assessor would evaluate the hazard — the properties of an organism that might cause harm to the environment — and the probability that it could establish itself in a particular environmental niche, reproduce, spread, and cause an adverse outcome. If there was certainty that an organism could not survive if it was released or escaped confinement, by definition it would pose no risk. However, given the uncertainties associated with evaluating risk, risk assessors generally say that if the organism is not likely to survive in a particular environment, then the risk of adverse outcomes is negligible. Because environmental risk assessment is highly dependent on both the particular organism in question and the particular environment into which it might be introduced, any assessment of the future risk of any genetically engineered organism must be conducted on a case-by-case basis.

Once risk is assessed, regulatory agencies then consider risk management. Risk management is the process of determining the appropriate restrictions or controls on a product or practice needed to reduce the risk to acceptable levels, often defined by law. This is referred to as "risk mitigation." Many U.S. laws incorporate some version of the standard of "unreasonable" risk, which, depending on the law, may include a weighing of benefits and costs in addition to risk. The standard of "unreasonableness" recognizes that some risk is associated with almost any product or activity and that absolute safety can never be assured. Mitigating risk to a "reasonable" level gives an agency some regulatory discretion and flexibility. It also recognizes that society has an interest in bringing useful products to market even if they pose some minimal risk. Some laws, however, place a higher priority on safety; for example, the Food, Drug, and Cosmetic Act applies a stricter "reasonable certainty of no harm" standard to products such as food additives and human and animal drugs.

those for more traditional recombinant DNA (rDNA) techniques; the biggest differences are in the size, scope, accuracy, and speed of genetic changes that can be accomplished.

Because synthetic biology in this context does not refer to a specific technology or type of product, but instead to enabling techniques, it is difficult to pinpoint when an organism should be called "engineered using synthetic biology." At its most rudimentary, a piece of DNA can be synthesized, identical in sequence to an existing gene, and inserted into an organism. Such an organism could also be constructed using traditional rDNA techniques, and even the scientists who produced the organisms may be unable to tell which was produced with which technology. However, as synthetic DNA constructs become more and more complex, often including several to dozens of genes and regulatory sequences in a single construct, it becomes nearly impossible to accomplish the same engineering feats through traditional rDNA technology. As gene synthesis becomes cheaper and gene circuits (complex interactions between multiple genes and regulatory sequences) become better understood, a wider variety of complex organisms will become much more easily attainable; this advancement is already apparent in research settings and has started penetrating into the marketplace.

An integral feature of synthetic biology that will enable rapid advancements in genetic engineering is the application of an engineering mindset to biology. Essential to this mindset is the ability of scientists and engineers to think of DNA not as strings of nucleotide base pairs (A's, T's, G's, and C's), but instead as parts, devices, and systems. These components can then be used and combined in new ways to achieve different outcomes. By developing and standardizing these tools and by thinking of DNA in this way, a diverse set of genetic variants can be designed, built, and tested more quickly. This approach also opens the door for people other than traditionally trained biologists to use genetic engineering for a broader range of applications.

However, it is important to distinguish between scientific capabilities to *synthesize* new genes, circuits, and genomes and the ability to *design* new genes, circuits, and genomes. While synthesis is becoming easier and cheaper, scientists are not yet in a position to design functional proteins that do not exist in nature and are still struggling to understand how to best build complex, functional new circuits (i.e., genes working together in a way that they may not have in nature). While synthetic biology is already allowing great strides in this area, genetic circuits incorporated into genetically engineered organisms will still be made up of naturally occurring genes for the near future. It is on these products containing mostly naturally occurring sequences that this report is focused.

Further into the future, the prospect of de novo production of whole genomes and recoding of whole genomes will become more common, particularly for microbes. In 2010, scientists at the J. Craig Venter Institute described the construction of the first "synthetic cell," a cell containing a fully synthetic genome based on the bacterial genome of *Mycoplasma mycoides* (Gibson, et al., 2010). Other groups have demonstrated the possibility of directed point mutations on the scale of entire genomes (Isaacs, et al., 2011). Even in these cases, re-design of the genome has been quite modest. Scientists still largely depend on nature to determine what will constitute functional biology. In the decades to come, it may become possible for scientists to design circuits and genes that are distinct from those

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found in nature.[2] While these advances will most certainly create additional challenges for the regulatory system when they are incorporated into commercial products, our focus in this study is on more immediate applications of synthetic biology. Just as the system in place for reviewing today's genetically engineered products has adapted to the scientific and technological advancements of the last 25 years, the regulatory system for the future must also adapt.

1.3 Methods

This report is the result of two years of research, conversations, and workshops on the challenges that may arise for the U.S. regulatory system as a result of the introduction of synthetic biology techniques. The first part of this study was approached with the goal of obtaining the most accurate assessment of how the U.S. regulatory system will review organisms engineered using synthetic biolo-

Box B: Definitions of Synthetic Biology

There are many ways to describe synthetic biology, in addition to the way it is described in this report. All of these descriptions are accurate, each with a different emphasis:

Royal Academy of Engineering (2009):

> *"Synthetic biology aims to design and engineer biologically based parts, novel devices and systems as well as redesigning existing, natural biological systems."*

President's Commission on the Study of Bioethical Issues (PCSBI, 2010):

> *"[S]ynthetic biology . . . aims to apply standardized engineering techniques to biology and thereby create organisms or biological systems with novel or specialized functions to address countless needs."*

The National Bioeconomy Blueprint (2012):

> *"Synthetic biology, the design and construction of new biological parts and systems, and the re-design of existing, natural biological systems for useful purposes, integrates engineering and computer-assisted design approaches with biological research."*

The Synthetic Biology Engineering Research Center, a multi-university research center funded by the National Science Foundation (SynBERC, 2013):

> *"Synthetic biology is the design and construction of new biological entities such as enzymes, genetic circuits, and cells or the redesign of existing biological systems. . . . The element that distinguishes synthetic biology from traditional molecular and cellular biology is the focus on the design and construction of core components (parts of enzymes, genetic circuits, metabolic pathways, etc.) that can be modeled, understood, and tuned to meet specific performance criteria, and the assembly of these smaller parts and devices into larger integrated systems that solve specific problems."*

2 In addition to new genes and circuits, advances may include genomes and cells that use non-natural biochemistry, such non-standard amino acids or nucleotides (also called xenobiology or orthogonal biology).

gy, including an exploration of any areas of uncertainty. We conducted a series of interviews with federal regulators to best understand how the regulatory system is applied today and to see what challenges, if any, they foresee in the near future.

To complement these interviews, outside legal experts were commissioned to analyze one of four hypothetical case studies of organisms engineered using synthetic biology. These case studies included:

- a plant with a highly modified chloroplast for use as an alcohol fuel feedstock (Bundy, 2012);
- microbes used for chemical production (in a contained facility) or for bioremediation (uncontained) (Mandel, 2012);
- algae used for biofuel production (Marchant, 2012); and,
- microbes used as drugs or cosmetics (Paradise & Fitzpatrick, 2012).

These case studies were chosen because they represent a variety of proposed, near-term uses of synthetic biology and because, collectively, they allowed an exploration of the primary U.S. agencies that regulate biotechnology: the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS), the U.S. Environmental Protection Agency (EPA), and the U.S. Food and Drug Administration (FDA).

Those four papers served as read-ahead materials for a preliminary meeting held in Rockville, MD, on January 30–31, 2012, that included the authors of the four case studies, a legal expert on food biotechnology, U.S. federal agency employees (including those that were previously interviewed), and the project investigators. This meeting and related discussions provided invaluable insight into the current U.S. Coordinated Framework for the Regulation of Biotechnology, how the Framework applies to organisms engineered using synthetic biology, and the challenges that may arise. To a lesser extent, these interactions provided a first look at some potential options that could be pursued to address those challenges.

Following the January meeting, a document was written summarizing initial perceptions of the key challenges that may arise in applying the current U.S. regulatory framework to organisms engineered using synthetic biology. Follow-up conversations with many of the meeting participants helped to resolve ambiguities and to ensure that our preliminary understanding was accurate. In addition, potential options to address these challenges began to be developed, researched, and consolidated.

We circulated the resulting document ahead of a workshop held in Washington, DC, on August 27–28, 2012. The purpose of the workshop was to broaden the discussion to a wide group of knowledgeable individuals and stakeholders and to gain feedback on the preliminary findings and potential options. This workshop included many of the legal experts and federal regulators from the preliminary meeting, plus additional federal employees, other outside science policy and regulatory experts, and perspectives from the do-it-yourself (DIY) biology community, the biotechnology industry, and a variety of non-governmental organizations with diverse opinions on synthetic biology and genetic engineering. Our goal was not to reach consensus among the members of this group, but rather to obtain an informed cross-section of viewpoints.

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Following this workshop, many of the participants were contacted to clarify points made at the workshop and to better understand viewpoints that were shared. Additional individuals were also sought for their perspectives, including some that were underrepresented in the workshop and conversations to date, e.g., experts in the regulation of traditional agricultural biotechnology.

This report is heavily informed by all of the individuals and groups that contributed throughout this two-year process. These individuals and groups are acknowledged at the end of this report. While we have tried to capture the variety of perspectives that we heard, this report does not represent any consensus nor does it present a comprehensive catalog of views.

Chapter 2: The Coordinated Framework for the Regulation of Products of Biotechnology

Genetically engineered products have been governed by a set of federal laws, regulations, and policies since the mid-1980s. The initial task for this study was to determine whether there are any differences between products engineered using synthetic biology and those using older genetic engineering techniques that would change their treatment under the U.S. regulatory system. If so, would the difference in regulatory treatment make any difference with respect to potential environmental, health, or safety concerns? We also investigated whether synthetic biology techniques will lead to the development of different kinds of products or a dramatic increase in the number of products that may challenge regulators.

As a starting point for this analysis, this section briefly reviews the regulation of products of genetic engineering in the United States. This analysis is limited to the health, safety, and environmental regulatory system, and does not address the broader economic, social, and ethical concerns that have been raised about the use of biotechnology.[3]

2.1 Policy for the Regulation of Genetically Engineered Products in the United States

Following the initial development of recombinant DNA (rDNA) techniques in the early 1970s, concerns about possible biosafety risks led to the development in 1976 of the National Institutes of Health (NIH) Guidelines for Research Using Recombinant DNA Molecules for laboratory researchers working with rDNA molecules. The NIH Guidelines continue to ensure that rDNA research funded by NIH is carried out under appropriate risk-based conditions of physical confinement to protect researchers and to prevent releases into the open environment (NIH, 2012; NIH, 2013).[4]

The NIH Guidelines successfully governed the initial phase of biotechnology research conducted in laboratories and other contained settings. By the mid-1980s, however, the commercial development of genetically engineered microbes and plants intended to be used as products in the environment led to a broad policy debate about the best ways to ensure that such applications did not harm human health or the environment.

This debate ultimately led in 1986 to the U.S. Coordinated Framework for the Regulation of Biotechnology, published by the White House Office of Science and Technology Policy (OSTP) (OSTP, 1986). The Coordinated Framework stated that existing federal laws appeared adequate for the regulation of products made with biotechnology, set out

By the mid-1980s, the commercial development of genetically engineered microbes and plants intended to be used as products in the environment led to a broad policy debate about the best ways to ensure that such applications did not harm human health or the environment.

3 The U.S. health, safety, and environmental regulatory agencies have limited authority and capacity to address non-physical harms such as social and ethical issues or economic conflicts. For the most part, those agencies focus on science-based assessments of risk and risk management. For example, FDA's regulation of genetically engineered animals considers, among other factors, the effect of the genetic changes on the animal's health, but does not consider the broader ethical concerns that have been raised by some critics about the application of genetic engineering to animals (PIFB, 2005a). Similarly, economic conflicts involving patenting of seeds and unwanted transgenic gene flow to conventional and organic crops are generally beyond the scope of risks addressed by these particular laws, although other federal and state agencies and laws may be involved (Center for Food Safety v. Vilsack, 2013).

4 The NIH Guidelines have been updated many times and continue to set standards for laboratory research involving rDNA. The most recent version now covers both rDNA and synthetic DNA (NIH, 2013; see Appendix).

the principal responsibilities of the U.S. federal regulatory agencies under existing laws, and stated that any regulatory gaps should be addressed by careful coordination among those agencies. The Coordinated Framework also acknowledged the need to evolve over time to take into account experience and advances in technology.[5] The Coordinated Framework noted that many products containing or derived from genetically engineered organisms – including food, new drugs, medical devices, biologics for humans and animals, and pesticides – would be reviewed by the relevant agencies "in essentially the same manner for safety and efficacy as products obtained by other techniques" (OSTP, 1986, p. 23304). At the same time, it noted that some genetically engineered microbes intended for use in the environment would require additional regulations under existing authority (OSTP, 1986, p. 23303).

The OSTP Policy Statement noted that genetically engineered organisms were not per se more risky than organisms developed through conventional breeding technology. While "information on the process could provide evidence of likely risk … the nature of the process could not be the sole or dispositive criterion for triggering oversight."

As agencies began to implement the Coordinated Framework, there were disagreements about the appropriate level of regulatory oversight for genetically engineered microbes, plants, and animals that were intended for release into the environment. As the Coordinated Framework had noted, new conventionally-bred varieties of plants, animals, and microbes had for years been routinely introduced into the environment without any regulatory oversight, other than for those that posed direct risks to plants or animals. Although new varieties of organisms produced through rDNA technology did not necessarily pose any more risk than those produced through conventional breeding techniques, the new technology created the opportunity to introduce genetic changes that were highly unlikely to occur in nature or through conventional breeding. Organisms engineered in this way would therefore be more likely to introduce novel traits into the environment, the impacts of which could be more difficult to predict. Given the concern that even small experimental releases of microbes, plants, and animals could result in environmental exposure if the organisms became established and spread, the additional uncertainty created by the development of organisms with novel traits argued for some regulatory review prior to any release of such organisms.

To clarify the regulatory oversight policy, OSTP issued a policy statement to guide agencies in developing regulations relating to genetically engineered organisms intended for release into the environment (OSTP, 1992). The Policy Statement directed agencies to exercise oversight "based on the risk posed by the introduction" and not "on the fact that an organism has been modified by a particular process or technique." Citing studies by the National Research Council, the Policy Statement noted that genetically engineered organisms were not per se more risky than organisms developed through conventional breeding technology. While "information on the process could provide evidence of likely risk … the nature of the process could not be the sole or dispositive criterion for triggering oversight." Instead, agencies should exercise oversight on the basis of the risk of the product's introduction into the environment, which would depend on a case-by-case assessment of the "characteristics of the organism, the target environment, and the type

5 In the Coordinated Framework, OSTP stated: "Although at the present time existing statutes seem adequate to deal with the emerging processes and products of modern biotechnology, there always can be potential problems and deficiencies in the regulatory apparatus in a fast moving field. The Working Group will be alert to the implications these changes will have on regulation, and in a timely fashion will make appropriate recommendations for administrative or legislative action" (OSTP, 1986, p. 23306).

of application." The Policy Statement directed agencies to regulate genetically engineered organisms intended for environmental release only when the evidence demonstrated that the introduction posed an "unreasonable risk."[6] OSTP concluded that genetically engineered organisms similar in risk to conventionally-bred organisms should be subject to no greater level of oversight than their conventional counterparts.

In response, federal agencies developed risk-based criteria that focused on those organisms for which hazard characterization indicated either increased risk or increased uncertainty regarding such risks. Under those criteria, low-risk genetically engineered organisms were exempted from regulation, including those that were used under containment or those that were well known through experience to pose a negligible ability to survive. Organisms developed through conventional breeding techniques were also generally exempted from regulation on the basis of long experience and the low likelihood of environmental exposure to novel traits.[7] The effect of the exemptions was, as a practical matter, to leave only genetically engineered organisms subject to review based on the potential of novel traits to have adverse environmental effects. As a consequence, most genetically engineered microbes, plants, and animals intended for use in the environment have been subject to federal regulatory review prior to any environmental release.

The principle that health and environmental risks should be assessed only case-by-case, based on the specific characteristics and intended use of the specific product, rather than on the process by which it is made, is a fundamental feature of U.S. biotechnology regulation that stands in contrast to the regulatory approaches of the European Union and some other nations (MacKenzie, 2000; Vogel & Lynch, 2001; PIFB, 2005b). Some parties have argued that the U.S. regulatory system's focus on science-based risk assessment and risk management is too limited, given the uncertainties about the risks posed by genetic engineering and the practical difficulty of "recalling" a living genetically engineered organism should there be unexpected adverse health or environmental impacts. A number of organizations have called for a more precautionary approach to the regulation of genetic engineering, including synthetic biology (FOE, 2012). The European approach to regulation of genetically engineered organisms reflects this precautionary principle. Combined with strong popular opinion against genetically engineered organisms, the result of the EU's regulatory policy is that few genetically engineered crops or foods derived from genetically engineered plants have been approved or commercialized. As noted previously, U.S. policy makers have rejected a process-based precautionary policy on the scientific argument that living products made with genetic engineering are not inherently more risky

Most genetically engineered microbes, plants, and animals intended for use in the environment have been subject to federal regulatory review prior to any environmental release.

6 As the OSTP noted in its 1992 Policy Statement, "Of course, in some cases an agency may not have sufficient information to determine whether the introductions of organisms would pose unreasonable risk, and whether additional oversight therefore would be warranted. In cases in which an agency has reason to believe that introductions could pose risk but lacks adequate information to determine if that risk is unreasonable, agencies may need to collect information" (OSTP, 1992).

7 For example, in the statement accompanying its final rules on plant-incorporated protectants, EPA justified its exemption of plant-incorporated protectants generated from sexually-compatible plants on the grounds that humans and the environment had long been exposed to such substances in nature and thus were likely to have adapted to that exposure. "The potential for novel, or significantly different environmental exposures to occur in such a situation, would be low" (EPA, 2001, p. 37800).

than those produced through conventional means (OSTP, 1986; OSTP, 1992).

2.2 Laws and Regulations Applicable to Genetically Engineered Products

Under the Coordinated Framework principles, products of genetic engineering are regulated under the same laws that apply to similar products produced through more conventional means. Determining what laws apply to which genetically engineered products therefore requires a review of the broad U.S. regulatory system for health, safety, and the environment.

The U.S. regulatory system is a mosaic of many laws, each of which has a different focus and scope and in many cases, different regulatory approaches. Each law differs in the kind and amount of authority it gives to a regulatory agency to assess and manage risks of concern. Some laws require a product to be approved by a regulatory agency before it can be sold, while other laws give authority for an agency to act only if there is evidence of harm after a product is on the market. (See Box C, Pre-Market vs. Post-Market Regulatory Authority.) Every law contains its own definition of products and activities subject to that law; definitions often refer to terms such as a product's characteristics, function, or intended use.

The three principal federal agencies responsible for regulating products developed with genetic engineering are the Department of Agriculture's Animal and Plant Health Inspection Service (APHIS), the Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA).[8] APHIS typically regulates field trials of genetically engineered crops and plants under its general authority to regulate plant pests, and reviews requests to "deregulate" the crop or plant, which, if granted, allows it to be grown without a permit at a commercial scale.[9] EPA regulates genetically engineered microbes as "new chemical substances" under the Toxic Substances Control Act (TSCA). EPA also regulates genetically engineered pesticides (including biopesticides and pesticides incorporated into plants) under its authority to regulate pesticides. FDA regulates products that fall under its broad authority to regulate food, food additives, human and animal drugs, and certain other products, including those that have been produced through genetic engineering. Each agency has developed regulations, guidelines, or guidances to help implement its authority under existing laws and to provide compliance advice for producers.[10] (For more detail,

8 There are numerous other laws and regulations that could apply in certain cases to products made through biotechnology or synthetic biology; we have focused only on the major ones here (CEQ & OSTP, 2001; PIFB, 2004).

9 Following field trials, developers who want to take a genetically engineered plant into commercial scale production typically petition APHIS for a determination of "non-regulated status," which is essentially a finding by APHIS that the plant is not likely to pose a plant pest risk at commercial scale and therefore is no longer subject to the Plant Pest Act. Once that determination is made by the agency, APHIS no longer has jurisdiction over the genetically engineered plant unless there is subsequent evidence showing it has plant pest characteristics.

10 Agencies have different means of interpreting and applying the laws that Congress has delegated to them for enforcement. Following the requirements of the Administrative Procedures Act and other statutory requirements, an agency may issue rules or regulations that are eventually codified in the Code of Federal Regulations. Rules and regulations are binding and violations usually carry penalties. Agencies may also publish non-binding advice in the form of "Guidances," which provide the agency's "current thinking" about a particular subject. See, for example, FDA, 2008. Other agencies also offer non-binding advice and guidance for compliance.

Box C: Pre-Market vs. Post-Market Regulatory Authority

Some laws require that certain types of products get pre-market approval from a regulatory agency before they can be sold. Many other products are not reviewed for safety before they are sold, but instead are subject to agency action to remove them from the market if they are causing harm. Human and animal drugs, food additives, and pesticides are examples of products that are subject to pre-market regulatory approval. Food, cosmetics, and dietary supplements are examples of products that can be sold without a prior regulatory safety review, but are subject to action if they cause harm. New chemicals are regulated under a system that provides for a pre-manufacturing notification to EPA but allows the chemical to go to market unless EPA finds there is unreasonable risk.

Under a pre-market approval process, agencies typically rely on the producer to provide all of the information the agency needs to approve the product; there are generally no time limits on how long the agency may take to make the decision. As a result, the pre-market approval process is typically relatively costly for producers. In addition to providing any information or conducting any studies that the agency might request, the approval process can keep a new product off the market for many years while the agency approval process continues.

A pre-market approval process gives an agency the greatest regulatory authority, since a producer must, as a practical matter, provide whatever information the agency requests as a part of its approval process. This allows the agency not only to review existing information as part of its risk assessment, but also to require the producer to develop new information to resolve areas where information may be unavailable or uncertain. Agencies can also use their pre-market authority to put conditions on its approval to further mitigate risk. For example, they can require warning labels to ensure that products are used safely, impose other use restrictions, and/or require producers to report any adverse events after the product is marketed.

However, most products marketed in the United States are not required to be reviewed or approved by a federal agency before they can be sold. Pre-market approval has not been seen by policy makers as being necessary or desirable for most products, because manufacturers have market incentives to sell safe products and are also legally liable for injury under common law, state product liability laws, and some federal laws. In addition, federal regulatory agencies can act to remove products from the market and levy penalties against the producer or distributor of harmful products. In such cases, the agency is required to gather evidence and may have to prove in court that a product is causing harm and the producer or distributor is violating the law. As a practical matter, manufacturers often voluntarily recall products when faced with the potential of litigation and adverse publicity. Post-market regulatory laws allow products to move to market more quickly and less expensively than pre-market approval regimes, but with some increase in the potential for harmful products to be sold for a period of time.

see the Appendix on Legal Authority for Biotechnology Products Under the Coordinated Framework.)

Figure 1 on page 21 summarizes our analysis of each federal agency's authority to evaluate and manage the potential risks of the products of genetic engineering, including those engineered using synthetic biology, under the current regulatory system. For the purposes of providing a comprehensive overview, the products reviewed in Figure 1 include

those derived from genetically engineered organisms (such as food and drugs), as well as genetically engineered plants, animals, and microbes intended for environmental release. The relevant risks include both the safety of the product for humans and animals, as well as environmental risks.

While most animals and microbes are covered if they have been genetically engineered, a plant that has been genetically engineered is covered only if it has been engineered using a listed "plant pest."

The rows are organized by type of product (including different types of organisms) and then by their characteristics or intended uses. The uppermost seven rows of Figure 1 (those rows corresponding to "Any product") show products for which the type of organism or the method by which it was made is irrelevant to its regulatory path. In these cases, products produced through genetic engineering are covered by the same regulatory authorities as conventionally-produced products and are treated no differently as a regulatory matter. Thus a drug produced by genetically engineered bacteria in bioreactors is held to the same standards of regulatory review and approval as a drug synthesized through more conventional chemistry. Products engineered using synthetic biology that fall into these rows will likewise be treated identically.

The bottom three rows list genetically engineered products that are regulated based either on the type of organism that has been engineered (microbes or animals) or on the fact that a product is genetically engineered (in the case of the voluntary review process under FDA for food).[11] It should be noted that while most animals and microbes are covered if they have been genetically engineered, a plant that has been genetically engineered is covered only if it has been engineered using a listed "plant pest."

The columns in Figure 1 indicate the main focus for decision making, the authority of each agency to consider risks outside of that main focus, and how broad the agencies' authorities are within that main focus. In the column on "Authority to consider potential risks outside of the main focus for decision-making," EPA is the only agency with broad authority to make regulatory decisions based on risks to the health and safety of a wide range of end-points, including humans, animals, and ecosystems (indicated by filled circles). Both APHIS and FDA are more limited in the environmental impacts that they can consider in their regulatory decision making; this is the case for any product, not just those that are genetically engineered. APHIS can deny a permit for a field trial or decline to deregulate a genetically engineered plant only on

11 Novel foods are not subject to a mandatory pre-market approval by FDA; instead, they are subject to FDA's post-market authorities only if a food is "adulterated," defined in part as containing substances that "may render" the food "injurious to health." Food derived from genetically engineered crops (e.g., corn and soybeans) is likewise not required to be approved by FDA, but FDA has encouraged developers to voluntarily meet with FDA officials and submit data showing that the food is as safe as food derived from conventionally bred sources (FDA, 1997). While FDA does not make a finding that the food is safe, it has the opportunity to raise questions which would, as a practical matter, prevent the food from being sold in the market because buyers demand that developers successfully answer those questions and complete the FDA consultation process. In effect, foods derived from genetically engineered crops go through a review process that does not apply to other novel foods. In 2001, FDA proposed making the consultation mandatory, but never implemented the proposal (FDA, 2001).

12 FDA has interpreted its authority to regulate the "safety" of animal drugs and food additives to apply not only to the safety of humans and the target animal, but also to "environmental effects that directly or indirectly affect the health of humans or animals as a result of FDA's allowing the new animal drug's 'use'" (CEQ & OSTP, 2001). For example, in its 1993 approval of Monsanto's recombinant bovine somatotropin to increase milk production in cows, FDA considered the impact of the approval on land use patterns, water quality, carbon dioxide emissions, and used syringe disposal.

the basis of the plant's potential to adversely impact plants or plant health. FDA could deny a permit under its "safety" authority only if an animal drug adversely affects the health of humans or animals.[12]

However, both APHIS and FDA are required under the National Environmental Policy Act (NEPA) to assess the broader environmental impacts of their actions (indicated by partially filled circles). Under NEPA, agencies are required to conduct an environmental assessment for significant federal actions, which include permits and approvals. If the agencies find in the assessment that the action would result in a "significant impact," NEPA requires the agency to complete an Environmental Impact Statement (EIS), which can be quite costly and time-consuming for the product developer. As a practical matter, the cost and regulatory delay required by an EIS provide a strong incentive for a developer to voluntarily agree to take mitigation measures needed to allow an agency to make a finding of "no significant risk." Although the agencies cannot require such risk mitigations as part of its regulatory decision, the NEPA assessment process provides some incentive for producers to voluntarily agree with such measures. In addition, the environmental assessment process also provides the agency and the public with important information about potential environmental impacts, even if it does not provide the agency with any additional legal basis for denying a permit based on adverse environmental impacts revealed in the EIS.

Figure 1 shows some unfilled circles in the column for "Authority to consider risks outside of the main focus for decision making," indicating that the regulatory processes for dietary supplements, cosmetics, and food contain no assessment or authority outside of the main focus for decision making. For dietary supplements and cosmetics, there is no pre-market approval process;[13] this is the case for conventional products as well as those that are genetically engineered or are derived from genetically engineered organisms. In the case of food, there is a voluntary pre-market consultation process (see footnote 11). Because these products may be sold without prior FDA review or approval, NEPA environmental assessments are not triggered. FDA's post-market authority is focused on human health and safety; as a result, FDA would be limited in its ability to address environmental risks that might arise from genetically engineered organisms used in, or for making, cosmetics, dietary supplements, and food. (These products are also discussed under "Additional Issues" in Chapter 4.)

The last three columns in Figure 1 indicate the applicable statute's authority for each product type at three different points in the regulatory process. The color of the boxes indicates the strength of each statute's authority within its main focus for decision making, as it is applied today: white indicates that there is no or virtually no authority, light gray indicates that the authority is limited or uncertain or that the authority has not been demonstrat-

13 A dietary supplement could include a substance, such as a sweetener, that would itself be regulated as a food additive; unless it is generally recognized as safe, it would be subject to FDA's pre-market approval process for food additives. In addition, the developer of a "new" dietary ingredient (NDI), defined as a dietary ingredient not sold in the United States before 1994, needs to notify FDA before it can market the supplement with the NDI and provide FDA with evidence that the supplement will "reasonably be expected to be safe." However, FDA does not make any finding about the safety of the NDI or the supplement.

ed, and dark gray indicates clear authority. In some cases, the light gray boxes have additional information that shows the source of the uncertainty or weakness of the statute. (For more discussion on legal uncertainty, see Chapter 4, Box E.)

These columns show that there is broad authority across all stages of the regulatory process for pesticides under EPA, and for human drugs, animal drugs,[14] and food additives under FDA.[15] If engineered using synthetic biology, human and animal drugs and pesticides would be subject to the same broad pre-market approval requirements.

The white boxes for dietary supplements, cosmetics and food reflect the fact that these products are subject to post-market enforcement and do not undergo mandatory pre-market risk assessments or approval processes. As noted previously, this regulatory approach does not mean that unsafe products are being sold; rather, it reflects the decision by policy makers that a post-market approach is sufficient along with other incentives and laws to ensure that manufacturers make safe products. Products in these categories made using synthetic biology techniques are unlikely to raise any greater risk or regulatory issues for FDA than similar products made by other means. (See "Additional Issues" in Chapter 4 for more discussion of these products.)

APHIS has broad authorities for pre-market assessment for field trials and during the deregulation process for plant products (dark gray boxes). Once a product is deregulated, however, APHIS officials require no reporting or other post-market follow-up (gray box) (Kuzma, et al., 2009). However, as discussed in more detail in Chapter 3, many engineered plants will no longer meet the definition of "regulated articles" under APHIS' plant pest authorities, a trend that is likely to be accelerated by synthetic biology and other emerging genetic engineering techniques (Kuzma & Kokotovich, 2011; Waltz, 2012; Pollack, 2014). For products that do meet the definition of a regulated article, the use of synthetic biology or more traditional engineering methods will not impact the regulatory path or create new challenges.

The regulation of intergeneric microorganisms is a second area that may pose a key challenge for the regulatory system going forward, as discussed in detail in Chapter 4. While EPA appears to have sufficient authority to request data and information on potential risks (indicated by a dark gray box), its authority to restrict or place conditions on the commercialization of a product or to address post-market concerns is, in our view, less certain (light gray boxes). This uncertainty applies to current genetic engineering technology today, but may pose even more of a problem in the future if synthetic biology leads

14 As indicated in Figure 1, FDA regulates recombinant DNA constructs inserted into animals and their residues as animal drugs. While FDA has broad pre-market approval authority over animal drugs, there has been some disagreement and ongoing controversy regarding whether this is the best approach to use for regulating genetically engineered animals (Mandel, 2004; PIFB, 2004; Jaffe, 2010). Concerns have been raised about the extent of public disclosure for animal drug approvals and about the ability of FDA to consider potential environmental impacts.

15 Under its authority to ensure the safety of human and animal drugs, FDA has the authority to oversee drug manufacturing facilities, and has issued "Good Manufacturing Practices" to provide guidance to manufacturers. However, as discussed in Chapter 3, FDA may not be able to regulate early field trials of plants that produce pharmaceuticals. As a result, the box in Figure 1 for drug manufacturing facilities under "Authority to test and assess potential risks (pre-market) is shaded grey.

Product type	With this intended use or characteristic	Meets this definition (under given statute)	Main focus for decision making under applicable statute	Authority to consider potential risks outside of main focus for decision making	Authority to test and assess potential risks (pre-market)	Authority to restrict use or marketing based on potential risk	Authority to address concerns that arise after the product is marketed
Any product, including modified plants, animals, and microbes	That will be used as a pesticide	Pesticide or Plant-incorporated protectant (EPA/FIFRA)	Human, animal & ecosystem health	●			
	That will be used as a drug	Drug or Animal Drug (FDA/FDCA)	Human & animal health	◎			
	That will produce a drug	Drug Manufacturing Facility (FDA/FDCA)	Human & animal health	◎	Early trials may lack oversight		
	That will be added to food and is not generally recognized as safe	Food additive (FDA/FDCA)	Human & animal health	◎			
	That will be used as or will produce a dietary supplement	Dietary Supplement (FDA/FDCA)	Human & animal health	○			
	That will be used as or will produce a cosmetic	Cosmetic (FDA/FDCA)	Human & animal health	○			
	That is a plant pest, uses a plant pest in its creation, or incorporates its DNA	Plant Pest or Regulated Article (USDA-APHIS/PPA)	Plant health	◎			
Any intergeneric microorganism	That will be used for any commercial purpose not listed above	Intergeneric microorganism (EPA/TSCA)	Human, animal & ecosystem health	●		See text	
Any gene(s) inserted into an animal	That will be used for any purpose	Animal drug (FDA/FDCA)	Human & animal health	◎			
Any modified organism	That will be used as a food	"Substantially equivalent" (FDA/FDCA)	Human & animal health	○	Voluntary process		

○ No authority; no assessment ◎ No authority; assessment under NEPA only ● Full authority over any potential risks

No authority | Limited or uncertain authority | Demonstrated Authority

Figure 1: Main focus and strength of regulatory authorities for genetically engineered products. For each statute, the main focus for decision making is listed (4th column). Circles represent the extent to which agencies can make decisions based on risks outside of that focus (5th column). Shaded boxes indicate the strength of authorities within that main focus (the final 3 columns).

Acronyms: APHIS (Animal and Plant Health Inspection Service), EPA (Environmental Protection Agency), FDA (Food and Drug Administration), FDCA (Federal Food, Drug, and Cosmetics Act), FIFRA (Federal Insecticide, Fungicide, and Rodenticide Act), NEPA (National Environmental Policy Act), PPA (Plant Protection Act), TSCA (Toxic Substances Control Act)

to an increase in the number and diversity of genetically engineered microbes. Apart from legal authority, this potentially rapid increase in genetically engineered microbes could strain EPA's resources. EPA officials have been able to ensure that appropriate risk mitigation measures have been taken for the limited number of genetically engineered microbes that have been reviewed to date, but it is not clear that they will be able to continue to do so in the future with current resources. (See Chapter 4.)

Most products engineered using synthetic biology will be regulated in the same way as products engineered using older genetic engineering techniques.

2.3 Products Engineered Using Synthetic Biology

Genetic engineering with synthetic biology methods is being used, and is being contemplated for use, for a wide variety of organisms and products that will largely fall into the product categories listed in Figure 1. Similar to earlier generations of genetic engineering, some of these applications will be used in contained environments to produce pharmaceuticals, fuels, or other chemicals. Other applications will involve genetically engineered organisms for use in the open environment. For example, corn and soybeans engineered by earlier methods are grown widely throughout the United States today.

Liquid transportation fuels are probably the most-promised and most-anticipated application of synthetic biology. Gasoline, diesel, or gases such as hydrogen could be produced using microorganisms as the factories themselves. These fuels might be produced in contained bioreactors (similar to the way ethanol is produced today) or in the environment. Genetically engineered algae, for example, is able to harness sunlight to produce fuels and would likely be grown in large ponds or other semi-contained facilities. The intent of genetic engineering these organisms is to adjust their metabolism to dedicate as much energy as possible to fuel production. EPA has already begun conversations with companies hoping to produce such fuel-producing microbes. Bioremediation and biomining are other probable uncontained uses of engineered microbes in the environment that would fall under EPA's purview (Wilson Center, 2012; Wilson Center, 2013).

Synthetic biology could also be used to modify plants that could then be used as feedstocks for biofuels, e.g., ethanol production. Product developers would engineer the plant to lower the amount of unfermentable material in the plant or to alter the plant material so that it is easier to turn into fuel. APHIS has already issued permits for field trials of plants with these properties (APHIS, 2013a).

There are many additional applications of synthetic biology where the engineered organisms are likely to be exclusively grown in contained bioreactors. For example, new biologically based materials could be produced with improved properties, such as being safer for the environment or safer for people who work with them. An example is an environmentally-friendly plastic that would be stable indoors, but would degrade into benign components when exposed to UV light in the outside environment (Philp, et al., 2012).

Synthetic biology is already actively being used for pharmaceuticals. The production of artemisinic acid (the precursor to the anti-malarial drug artemisinin) is probably the most well-known application of synthetic biology (Peplow, 2013). The company Amyris has now shown that it is possible to scale-up production of the chemical to a level where the drug can be made easily available (Amyris, 2013).

The rapid production of vaccines upon the emergence of a new human or animal microbial pathogen is a likely new direction for synthetic biology. A group including scientists from the J. Craig Venter Institute and Novartis recently demonstrated the generation of influenza viruses using only the virus' DNA sequences. Using synthetic biology methods, vaccinologists will be able to construct specific vaccine seed viruses rapidly, cutting weeks or perhaps months from the current interval between virus identification and vaccine availability (Dormitzer, et al., 2013). Such a vaccine falls under FDA's strong pre-market and post-market authorities.

While organisms engineered using synthetic biology will have many new applications, most products engineered using synthetic biology will be regulated in the same way as products engineered using older genetic engineering techniques, under the same laws and regulations shown in Figure 1 and explained in greater detail in the Appendix. Whether an organism is engineered using synthetic biology or older genetic engineering techniques, the U.S. regulatory agencies will be addressing the same types of health and environmental concerns.

Synthetic biology is, however, likely to make it much easier to introduce novel genetic sequences and traits into microbes, plants, and animals intended for use in the environment. While such products do not necessarily pose more or different environmental *risks* than organisms engineered by other means, the novelty of the traits made possible by the technology may create more *uncertainty* about the organism's environmental impacts. To prevent an unwanted organism from becoming established, regulatory agencies have, to date, assessed potential environmental risks before a genetically engineered organism is sold.

As discussed in the following chapters, APHIS's ability to review plants engineered using synthetic biology may be compromised since synthetic biology may facilitate the production of novel plants that do not fall within APHIS's legal authority over plant pests. For EPA's TSCA Biotechnology Program, a challenge will be its ability to keep pace with the anticipated rapid development of novel genetically engineered microorganisms made possible by synthetic biology. The agency's authority to regulate microorganisms intended for use in the environment may also need to be strengthened, although EPA probably has sufficient legal authority to address potential environmental risks.

Chapter 3: Regulating Plant Products Engineered Using Synthetic Biology

One of the key challenges that the U.S. biotechnology regulatory system will face in the near future is in the regulation of engineered plants by USDA's Animal and Plant Health Inspection Service (APHIS). This challenge arises because APHIS' authority to regulate genetically engineered plants depends on the use of plant pests during their development. Though the use of plant pests has been the mainstay of plant genetic engineering over the past two decades, other methods that perform the same function, but which do not require plant pests, are increasingly being used (Waltz, 2012). As newer engineering techniques, including synthetic biology, become more widespread, they will increasingly give product developers options to develop new genetically engineered plants that are not subject to review by APHIS.

Unlike other agencies that have responsibility over genetically engineered organisms, APHIS' authority over genetically engineered plants turns primarily on a technique: the use of plant pests or some component of plant pests in the genetic engineering process.

3.1 Key Challenge

Synthetic biology and other new genetic engineering techniques will likely lead to an increase in the number of genetically engineered plants that will not be subject to review by USDA, potentially resulting in the cultivation of genetically engineered plants for field trials and commercial production without prior regulatory review for possible environmental or safety concerns.

APHIS' authority to review genetically engineered plants is derived from its legal authority to control plant pests.[16] Concerned that using genes from known plant pests might introduce plant pest characteristics into an engineered plant,[17] USDA decided in the mid-1980s that plants that had been engineered using a known plant pest as a recipient, source or donor organism, or as a vector or vector agent, should be regulated as "presumptive" plant pests (APHIS, 1987; see the Appendix for more details). As a result, unlike other agencies that have responsibility over genetically engineered organisms, APHIS' authority over genetically engineered plants turns primarily on a technique: the use of plant pests or some component of plant pests in the genetic engineering process.

Under APHIS' regulations, plants that have been genetically engineered using plant pests in the engineering process (called "regulated articles"[18] in APHIS' rules) cannot be planted in field trials unless the developer has either notified APHIS in the case of defined low-risk plants or alternatively has received a permit

16 A "plant pest" is defined in APHIS' regulations as "any living stage" of an organism that "can directly or indirectly injure or cause disease or damage in or to any plants or parts thereof, or any processed, manufactured, or other products of plants" (7 C.F.R. § 340.1). This definition is taken from the Federal Plant Pest Act under which APHIS' rules were originally issued. The later Plant Protection Act (7 U.S.C. § 7701 et seq.), enacted in 2000, consolidated several USDA laws and contained non-material changes to the definition of "plant pest."

17 One of the earliest and still one of the most common methods used by plant biotechnologists for incorporating desired genes into plants is to use plant pests (mostly plasmid vectors from *Agrobacterium tumefaciens*). Also, DNA sequences from plant pests have often been incorporated into genetically engineered organisms (e.g., the cauliflower mosaic virus transcriptional promoter).

18 APHIS defines "regulated article" in its regulations (7 CFR § 340.1). In addition to including organisms engineered with the use of known plant pests, the definition also covers any genetically engineered organism that APHIS has "reason to believe" is a plant pest and organisms whose "classification is unknown." This latter definition could be interpreted to allow APHIS to regulate novel genetically engineered organisms even when a plant pest has not been used as part of the transformation process, if it is "unknown" whether the novel organism is a plant pest. This position was taken by USDA's Associate General Counsel John Golden in Congressional tes-

from APHIS. Permits contain conditions for field trials that are intended to limit or prevent the movement of the experimental transgenes from the field trial sites. After testing, if a developer intends to commercialize the genetically engineered plant, it can petition APHIS to "deregulate" the plant; that is, have APHIS determine that the plant is not likely to pose a plant pest risk. Since APHIS' authority is limited to regulating plant pests, once it has determined that a genetically engineered variety is not a plant pest, it no longer has legal authority to regulate the plant (Center for Food Safety v. Vilsack, 2013). As discussed below, certain plants may also be regulated by FDA or EPA, but APHIS has traditionally overseen the early stages of product development even in these cases.

Once a plant is under review by APHIS as a presumptive plant pest, APHIS is also separately required by the National Environmental Policy Act (NEPA) to consider broader environmental and economic impacts before issuing permits for field trials or deciding to deregulate. (See the discussion about NEPA in Chapter 2.) APHIS has authorized thousands of field trials of genetically engineered plants since the rules were finalized in 1987 and has overseen the deregulation process for 95 genetically engineered crops as of August, 2013 (APHIS, 2013a; APHIS, 2013b).

APHIS has sometimes been described as being responsible for regulating the potential environmental risks of genetically engineered crops (Chassy, et al., 2001). As a legal matter, however, APHIS' role is distinctly more limited. Although APHIS gathers information on a broad array of environmental and economic risks as part of the deregulation process, its sole authority to regulate rests on the potential of a plant to be a plant pest – an organism that causes physical injury to other plants. APHIS has no authority under its plant pest authorities to make regulatory decisions based on impacts such as increased weediness or invasiveness, undesired gene flow to unmodified crops, increased herbicide use, or other environmental or economic impacts (Center for Food Safety v. Vilsack, 2013).

Nevertheless, as noted below, APHIS has played an important role in reviewing and limiting the undesirable effects of proposed genetically engineered plants. As a result, the development of new plant transformation techniques that can produce new genetically engineered plants that will not be reviewed by APHIS raises significant policy issues.

In recent years, as genetic engineering technology has developed, it has become possible to reliably introduce novel traits into plants through genetic engineering techniques that do not involve the use of known plant pests in the transformation process. In such cases, USDA has taken the position that it has no legal authority to review the plant.[19] The APHIS website displays 17 "Regulated Letters of Inquiry" from product and technology developers from July, 2011, through March,

In recent years, as genetic engineering technology has developed, it has become possible to reliably introduce novel traits into plants through genetic engineering techniques that do not involve the use of known plant pests in the transformation process. In such cases, USDA has taken the position that it has no legal authority to review the plant.

timony in 1986 (Committee on Science, 1986, pp. 114-115). In effect, this interpretation would shift the burden of proof to a developer to prove that a new plant variety is not a plant pest, rather than requiring the agency to demonstrate that a plant is a plant pest or that there is "reason to believe" that it is a plant pest (Bundy, 2012). As noted in the text, recent advisory letters from APHIS take a narrower interpretation of its authority.

19 For example, in its letter to BioGlow LLC dated March 21, 2013, APHIS concluded, "No plant pests, unclassified organisms, or organisms whose classification is unknown are being used to genetically engineer these plants. In addition, APHIS has no reason to believe these plants are plant pests. Therefore, APHIS does not consider these GE plants … to be regulated under 7 CFR part 340" (APHIS, 2013c).

Box D: An engineered plant not reviewed by APHIS

One of the APHIS Letters of Inquiry is a January, 2012, letter from Ceres, Inc. (APHIS, 2013d) This case underscores many of the issues that are beginning to arise in the U.S. regulation of engineered plants. The letter describes Ceres' engineered switchgrass variety with increased biomass and more fermentable sugars for use as a biofuel feedstock. This switchgrass contains two transgenic genes, plus regulatory sequences and short synthetic sequences used to facilitate insertion of the genetic construct into the plant. This product is unregulated by APHIS because it does not contain any plant pest sequences nor was a plant pest used in the transformation process; Ceres used a biolistics (gene gun) method instead. Since it is not covered by any other regulations, it will not undergo pre-market regulatory review or an environmental assessment under NEPA by any U.S. agency.

This product also illustrates an important point about the types of plants and applications that newer generations of biotechnology product developers will pursue. While older genetic engineering techniques were used primarily to improve food crop yields, generating biofuel feedstocks may become an increasingly important part of the industry. The plants that are being considered for use as biofuel feedstocks (often fast-growing, semi-domesticated perennials like switchgrass) are different from the crops (primarily corn, soybeans, and cotton) that have traditionally been the focus of biotechnology development, assessment, and regulation. Furthermore, many plants that may be most suitable for biofuel feedstock production in the United States, including switchgrass, are species native to large portions of the country (or interbreed easily with such native species), creating additional challenges for environmental risk management.

2013 seeking APHIS' opinion on whether their genetically engineered plant is subject to APHIS' regulations. (For one illustrative example, see Box D.) In response to about half of these inquiries, APHIS indicated that the specific product or the technology described did not fall under its "regulated article" definition because plant pests were not used in the process of inserting genetic material and there was no other "reason to believe" that the engineered plant was a plant pest (APHIS, 2013d). Such responses are made by APHIS on a case-by-case basis. This trend may well be accelerated by the use of synthetic biology and other emerging genetic engineering techniques (Waltz, 2012).[20]

With new genetic engineering methods that fall outside USDA's regulatory authority, developers will increasingly be able to choose to develop new plant varieties through methods that are not subject to any APHIS review or permit requirements. This may be especially true for products that are not intended for food or feed (e.g., biofuel feedstocks), for which the market may not demand as stringent oversight.[21] Furthermore, such products would not be subject to NEPA review or,

20 Included among the Letters of Inquiry are plants engineered using biolistic methods and protoplast fusion, rather than plant pests.

21 As noted in footnote 11, developers of genetically engineered food and feed crops are effectively required by the market to comply with FDA's voluntary pre-market consultation process. Grocery manufacturers and other food and feed processors who buy bulk grain are particularly sensitive to the need to ensure that ingredients that go into their food products are safe.

under the current regulatory framework, pre-market review by any other federal agency unless they contain pesticidal substances covered by EPA under its authority over pesticides.

An example that has received recent publicity is a crowd-funded project by hobbyist scientists to distribute seeds for plants that have been engineered to include a gene for bioluminescence (Pollack, 2013). Since the developers are planning to avoid the use of plant pests in engineering the plant, USDA would likely have no jurisdiction for regulating the distribution or planting of the engineered seeds. No Letter of Inquiry for this particular plant has been posted on APHIS' website.

Allowing genetically engineered plants to be cultivated in the environment without prior regulatory review would mark a substantial change in the U.S. regulatory system and would impact a broad range of plant products. Under the current system, field trials for most genetically engineered crops have been conducted under either notification (for low-risk plants) or under APHIS permits, which have required physical and biological containment to minimize the potential for transgenes to move from the field test site. APHIS requires containment to prevent the unintended spread of genes that could have a plant pest effect, but its requirements also have the practical effect of preventing the unintended spread of undesirable transgenes into food and feed crops.[22]

Both FDA and EPA rely upon APHIS' regulation of early field trials to support their own regulatory frameworks for genetically engineered plants; if genetically engineered plants are grown without APHIS review, it may be difficult for those agencies to impose similar containment requirements. For example, APHIS requires that genetically engineered plants intended to produce pharmaceutical or industrial compounds can be grown only under permit (APHIS, 2003a; APHIS, 2003b), and FDA has depended on this APHIS permitting process to ensure appropriate oversight.[23] FDA has no authority of its own over field trials of plants that produce a new pharmaceutical until the product is submitted as an "investigational new drug," which generally occurs at the beginning of clinical trials or preclinical investigation, a stage that may come well after the plant has been cultivated in the environment. At that point, FDA will likely have the authority to regulate the plant as a drug manufacturing facility and therefore may be able to require containment procedures. Plants producing already-approved drugs may also be regulated as drug manufacturing facilities; it is not clear when this authority would begin, but it is likely to be at the beginning of commercial-scale production, well after initial field trials. Furthermore, as mentioned in Chapter 2, FDA's new animal drug and its

Both FDA and EPA rely upon APHIS' regulation of early field trials to support their own regulatory frameworks for genetically engineered plants.

22 In 2002, USDA quarantined a half-million bushels of soybeans that had been mixed with materials from corn plants genetically engineered to produce a pharmaceutical compound (Becker & Vogt, 2003). Noting the potential for field trials to result in low levels of unapproved transgenes in the food supply, the Office of Science and Technology Policy in 2002 announced actions to strengthen APHIS' field trial requirements and to establish procedures for early assessments of the food safety of novel proteins produced by genetically engineered plants (OSTP, 2002). Even if low levels of transgenes do not pose food safety risks, food manufacturers may be reluctant to accept such material.

23 A Draft Guidance issued by FDA in 2002 states that "Because bioengineered pharmaceutical plants will be grown under APHIS permit, and because such permits enabling field trials will be obtained prior to submission of a product application, APHIS/BRS [APHIS' Biotechnology Regulatory Services] will identify and evaluate the potential environmental effects posed by field growth of such plants" (FDA, 2002).

food additive authorities reach only to human and animal health; even with a broad interpretation of safety, FDA cannot regulate based solely on environmental harm such as the risks to genetic diversity in plants.[24]

Similarly, plants engineered to produce a pesticide are regulated by APHIS at early stages of product development. Only when the product developer wants to plant more than 10 acres does EPA's oversight under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) usually begin. At that point, EPA likely has the authority to enforce risk management procedures, such as refugia requirements to prevent insect resistance. EPA can require an experimental use permit for smaller tests if insufficient containment is present to prevent the plant-incorporated protectant (i.e., the pesticide expressed by a transgene) from entering food or feed supplies (EPA, 2012a). In the absence of APHIS authority, EPA could likely amend its rules to require containment for all field tests of plant-incorporated protectants.

This lack of APHIS authority may also create a "Catch-22" for university researchers developing newer generations of engineered plants.

While statutes covering pharmaceuticals and pesticides provide FDA and EPA with some authority over field trials of some engineered plants (albeit later in the process than APHIS' authorities have traditionally reached), plants that produce industrial chemicals have no oversight outside of APHIS' authorities. EPA's Toxic Substances Control Act (TSCA) would likely capture the produced chemical itself, but the plant would not receive any assessment and would not have to comply with any regulatory risk mitigation measures. EPA has previously stated that it has the statutory authority under TSCA to regulate engineered plants (CEQ & OSTP, 2001), but it has not to date indicated any desire to do so in light of APHIS' comprehensive regulatory review. The possibility of capturing engineered plants under TSCA is described in more detail in Option 4, below.

In addition to regulating field trials, APHIS reviews genetically engineered plants for their potential to pose plant pest risks before they are allowed to be grown on a commercial scale. As required by NEPA, APHIS also assesses broader environmental risks and makes that information available as part of the deregulation petition process. If APHIS determines that the plant is not likely to pose a plant pest risk, APHIS no longer has the legal authority to regulate it (Center for Food Safety v. Vilsack, 2013). As part of its plant pest risk assessment, APHIS considers indirect effects on plant health, such as the potential impact of a plant on beneficial insects such as pollinators, but how far APHIS can go in considering indirect effects is not clear. Despite the limited basis for the regulatory decision, the deregulation process does have the benefit of providing public information about environmental and economic impacts. Non-pesticidal, genetically engineered plants not regulated by APHIS would receive no regulatory review for any environmental risks before being grown at commercial scale.

This lack of APHIS authority may also create a "Catch-22" for university researchers developing newer generations of engineered plants. To comply with NIH Guidelines, university researchers can grow engineered plants developed in the lab in field trials only under the approval of a federal regulatory agency

24 To ensure the safety, quality, and efficacy of the drug, FDA could impose strict containment requirements to avoid contamination of the drug from other environmental sources and thereby indirectly "protect" the environment as well. Implementing such requirements could also trigger a NEPA environmental assessment process.

with jurisdiction over the field trial.[25] But if there is no agency with jurisdiction, university researchers cannot grow the engineered plants in the field without violating the NIH Guidelines, and thus jeopardizing future federal funding.[26] This situation could leave these researchers in a position in which they are unable to find appropriate regulatory oversight and so cannot perform their experiments.

3.2 Policy Options

Below, we present four options to address this key challenge, each of which is discussed briefly along with important aspects and issues to consider. The first option presents ways that voluntary systems could augment the current regulatory system. Options for enhancing APHIS' authority include expanding its existing authorities (such as those concerning noxious weeds) to genetically engineered plants or passing new legislation that would give APHIS new tools for review and regulation. The final option raises the possibility that EPA could apply its authorities under FIFRA or TSCA to genetically engineered plants.

Option 1: Maintain existing regulatory system and rely on a voluntary approach for those genetically engineered plants not subject to review.

For twenty-five years, APHIS has required that developers of virtually all genetically engineered plants either notify APHIS (in the case of low-risk releases) or obtain a permit prior to field trials outside of contained facilities. In addition, genetically engineered plants grown at commercial scale have been "deregulated" by APHIS. As a result, APHIS has been able to conduct a risk assessment and impose risk mitigation measures before genetically engineered plants have been released in the environment.

However, some argue that experience over the past twenty-five years has shown that genetically engineered plants pose negligible health or environmental risks, that plant biotechnology is over-regulated, and that regulations are costly and prevent beneficial new products from coming to market (Miller & Conko, 2004). In this view, the oversight performed by APHIS to date has served its purpose, and it may be time for such regulatory review to be phased out. This option would allow new genetically engineered plants that are not covered by APHIS' current rules to be grown without prior regulatory review in the same manner as conventionally-bred new varieties of plants and crops.

APHIS could maintain a voluntary pre-market assessment process, similar to the current APHIS procedures, for all engineered plants that pose no plant pest risks.

APHIS could maintain a voluntary pre-market assessment process, similar to the current APHIS procedures, for all engineered plants that pose no plant pest risks. This process could include voluntary consultations for field tests to promote isolation and to prevent loss of confinement.[27] The voluntary assessment

25 The NIH Guidelines are focused on containment and have no provisions for deliberate environmental release of engineered organisms. Under the Guidelines, a researcher could not test a genetically engineered organism outside of a contained facility unless the release was specifically approved or authorized by a federal regulatory agency such as APHIS or EPA under Section I-A-1 of the NIH Guidelines (NIH, 2013).

26 The NIH Guidelines are not regulations per se, but they are mandatory for those subject to them, have been incorporated into many other mandatory processes, and play an important role in ensuring the safe use of genetically engineered organisms. When an institution receives any funding for recombinant or synthetic DNA research from NIH, all such research performed at the entire institution must comply with the NIH Guidelines (Section I-C-1-a-(1)) (NIH, 2013). If those requirements are not met, NIH financial support could be withdrawn from the entire institution carrying out the research. It should also be noted that most, if not all, federal agencies that provide funding for recombinant or synthetic DNA research also require compliance with the NIH Guidelines.

process provides several advantages to industry, including enhanced public trust, and so product developers may opt to participate in this process. Furthermore, similar voluntary regimes in other contexts have become de facto mandatory practices; for example, genetically engineered food crops typically go through FDA's voluntary consultation process for foods derived from genetically engineered crops. (See footnote 11.) It is not clear, however, if risks to the environment (rather than food safety) would drive market demand for oversight.

OSTP could lead an interagency effort to evaluate how APHIS can best apply its existing authorities to assess and mitigate the risks of concern from the next generation of plants engineered with synthetic biology and other newer genetic engineering techniques.

Alternatively, product developers could choose to depend on industry-developed standards to ensure that environmental risks are assessed and addressed. However, some would object to making such a review voluntary or subject only to industry-created standards and may question the rigor of this approach. Also, such a system may leave many university researchers without appropriate regulatory oversight to satisfy requirements under the NIH Guidelines, preventing useful research from being conducted.

Option 2: Identify the most likely risks from newer generations of plant biotechnology and apply existing laws best able to mitigate them.

OSTP could lead an interagency effort to evaluate how APHIS can best apply its existing authorities to assess and mitigate the risks of concern from the next generation of plants engineered with synthetic biology and other newer genetic engineering techniques. FDA and EPA should be included in the effort as they are partners with APHIS in the regulation of genetically engineered plants and depend on APHIS' permitting of early field trials.

Given the recent interest in biofuel production, genetic engineering is being applied to highly productive, robust, semi-domesticated, perennial plants. For such products, enhanced weediness may be a primary concern, thus APHIS' existing authority over noxious weeds may be a logical approach. Because the definition of "noxious weed" includes a broad range of harms, including "damage to the natural resources of the United States, the public health, or the environment,"[28] the scope of harms that APHIS could review using these authorities is much broader than in the current plant pest-based system.

In 2008, APHIS proposed a rule that would allow the agency to evaluate engineered plants for their potential both as a plant pest

27 Since NEPA assessments are triggered by federal action, products within a voluntary system are not required to undergo any NEPA review. For example, the FDA voluntary consultation process for food safety does not trigger NEPA. While a voluntary consultation process with APHIS could include many of the environmental concerns that a NEPA assessment usually covers, products may not be held to as rigorous a review. In addition, as noted previously, compliance with NEPA provides additional incentives for developers to voluntarily undertake risk mitigation measures and provides the agency and public with additional information about potential environmental impacts. For this reason, taking away the necessity for NEPA compliance will likely be opposed by those who believe that NEPA is an important tool in assessing and managing the potential environmental risks of genetically engineered plants.

28 A noxious weed is defined as "any plant or plant product that can directly or indirectly injure or cause damage to crops (including nursery stock or plant products), livestock, poultry, or other interests of agriculture, irrigation, navigation, the natural resources of the United States, the public health, or the environment" (APHIS, 2008).

and as a noxious weed. In proposing the rule, APHIS noted that "[T]echnological advances have led to the possibility of developing GE organisms that do not fit within the plant pest definition, but may cause environmental or other types of physical harm or damage covered by the definition of noxious weed in the [Plant Protection Act]" (APHIS, 2008). This proposed rule has not advanced, but it represents one way that APHIS could maintain authority over most genetically engineered plants. One advantage to this option is that it allows APHIS to continue to function in the same relationship with plant developers as it has for the last twenty-five years as the early-stage regulator for genetically engineered plants and crops, minimizing disruption for the industry and other federal regulatory agencies.

An OSTP-led interagency review effort could evaluate the effectiveness of this and other options. Few plants are considered by APHIS to be plant pests or noxious weeds, and there is little scientific basis to believe that most genetic engineering will increase plant pest or noxious weed risks compared to the conventional plant.[29] In effect, APHIS would be using its plant pest and noxious weed authorities as legal levers to be able to review and regulate the environmental risks of genetically engineered plants. That regulatory role may be important, but stretching existing legal authority to achieve it might create additional confusion and uncertainty.

For example, the 2008 Proposed Rule introduced a tiered approach whereby low-risk plants would be quickly reviewed, while plants that posed the greatest risk would undergo the most stringent review. However, the definition of noxious weed is quite broad, thus APHIS would have to detail the potential harms that will fall under each tier. Furthermore, the standards that would have to be met and the regulatory fate of plants that do not meet those standards would have to be well defined. In particular, APHIS authorities over noxious weeds currently refers to a list of noxious weeds that has so far been restricted to plants that have proven to cause severe damage and to be very difficult to remove from the environment (APHIS, 2008).

Addressing these challenges will be difficult, and it is likely that the details included in a new proposed rule will determine how well it is received and, ultimately, how well such a system will function. Since this option could represent a major rule change to how engineered plants are regulated, the agency's rule-making process would be under much scrutiny.

Option 3: Give APHIS additional authority to review and regulate genetically engineered plants.

If current authorities under APHIS are found to be lacking in their ability to oversee plants that pose potential environmental risks, then Congressional action could be taken. The goal would be to expand APHIS' authority to review genetically engineered plants beyond those that may pose some plant pest risks, regardless of the techniques used to engi-

Because the definition of "noxious weed" includes a broad range of harms, including "damage to the natural resources of the United States, the public health, or the environment," the scope of harms that APHIS could review using these authorities is much broader than in the current plant pest-based system.

29 Only a few parasitic plant species, such as striga, witchweed and dodder, are listed by APHIS as plant pests, and only 98 aquatic, terrestrial or parasitic plant species are so invasive, damaging, and difficult to control that APHIS has listed them as noxious weeds (APHIS, 2008). In general, these are not traits that developers would be trying to intentionally breed into plants. To date, APHIS has not denied any petition for deregulation on the basis that the genetically engineered plant has a greater plant pest risk than its conventional counterpart.

neer the plant. Such action could bring the regulation of genetically engineered plants into better alignment with the regulation of genetically engineered microbes and animals. As discussed in Chapter 2, most microbes and animals fall under regulation (by EPA or FDA, respectively) if they have been genetically engineered.

Congress could give USDA broad authority to review many types of genetically engineered plants for a wide range of environmental harms, similar to EPA's broad authority to review genetically engineered microbes.

Congress could choose to define a set of traits that it finds undesirable and give USDA authority to regulate based on that definition. This would be similar to, and could have many of the same challenges as, authorities based on plant pests or noxious weeds. Alternatively, Congress could give USDA broad authority to review many types of genetically engineered plants for a wide range of environmental harms, similar to EPA's broad authority to review genetically engineered microbes. Such an approach would give USDA discretion in how it chooses to regulate these plants and could provide more certainty to product developers and the public. However, this would be viewed by many as a departure from the Coordinated Framework's stated principle that living products made using genetic engineering are not inherently more risky than those produced through conventional means. (See Chapter 2.)

In either of these cases, USDA would have the authority to review genetically engineered plants according to their likely level of risk, including exemptions for low-risk plants. Once a plant has been reviewed, APHIS could deregulate it, as it currently does, or approve it for commercialization. One practical challenge to implementation would be to describe the end points upon which APHIS should regulate; an environmental health focus may be difficult for APHIS to incorporate into its current regulatory purview over plant and animal health.

Congress could also consider looking to the regulatory systems of other nations as possible models (MacKenzie, 2000; Vogel & Lynch, 2001; McHughen, 2007). For example, Canada regulates plants with "novel traits" under the Canadian Food Inspection Agency. In practice, this standard has included all genetically engineered plants, although other modification methods, including traditional breeding, can generate novel traits and so fall under this regulatory authority. These plants undergo pre-market review that includes assessments of a wide range of environmental risks (Canadian Food Inspection Agency, 2012). This approach is reasonably consistent with the science-based and technology-neutral policy of the U.S. biotechnology regulatory system, in that it focuses on potential harms of a novel trait, without regard to how the trait was introduced in the plant. If a system like this was adopted in the United States, plant breeders who use conventional breeding technologies would likely object to being subject to regulation and would argue that there is little justification to do so.

The European Union uses genetic engineering as a trigger for regulatory review and has adopted a precautionary approach with every plant undergoing extensive review regardless of the extent of health or environmental risk the specific product is thought to pose. Such a system, however, has proven to be extremely onerous to product developers, with very few products having been approved. It also represents a significant departure from established risk-based principles of U.S. regulatory policy, making it an unlikely candidate for serious consideration.

Any Congressional action to change APHIS' authorities would likely spur significant interest (and conflict) among stakeholders.

Option 4: Promulgate rules under FIFRA or TSCA for EPA to regulate engineered plants.

This option increases the role of EPA in the regulation of plant biotechnology, which would represent a major departure from the current regulatory system and, more broadly, in the traditional roles of EPA and USDA. Arguably, however, both FIFRA and TSCA give EPA authority over DNA sequences inserted into genetically engineered plants (in the case of FIFRA)[30] or over the genetically engineered plants themselves (TSCA). Both FIFRA and TSCA give EPA authorities over a broad range of potential risks, including environmental concerns.

Under EPA's pesticide statute, FIFRA, the definition of "pesticide" includes "plant regulator," which refers to any substance that changes the growth or behavior of a plant.[31] That definition could be interpreted to include many, if not all, DNA sequences used for plant biotechnology. EPA could promulgate a new rule under FIFRA describing how it defines "plant regulator" and the boundaries of its authority.[32] However, FIFRA may not be the most appropriate statute for the regulation of all or most genetically engineered plants. Since pesticides are designed to be toxic to the pests that they target, the risk assessment process under FIFRA is very stringent and begins with an assumption of some risk to humans or other non-target organisms. It is therefore up to the product developer to demonstrate that the pesticide can be used safely. However, most inserted sequences in genetically engineered plants are not intended to produce toxic proteins, leading to a mismatch between the burden placed on product developers and the potential risk inherent in the product.

It would also be possible for EPA to claim authority over these plant products using its authorities under TSCA. Under TSCA, EPA's definition of "new chemical substance"[33] is broad enough that it could include new genetically engineered varieties of plants or animals, and EPA has consistently maintained that it has this authority (CEQ & OSTP, 2001). If EPA chose to apply these authorities to genetically engineered plants, it would need to promulgate a new rule that defined which plants it would regulate, which would be exempt, and the procedures that would be followed. It is not clear how this option would be perceived by biotechnology stakeholders, but it should be noted that plant product developers have worked with APHIS for many years and have developed a level of familiarity with the agency that does not necessarily extend to EPA, although it could in due course.

Arguably, both FIFRA and TSCA give EPA authority over DNA sequences inserted into genetically engineered plants (in the case of FIFRA) or over the genetically engineered plants themselves (TSCA).

30 FIFRA is currently applied to genetically engineered plants only with respect to "plant-incorporated protectants," which includes DNA sequences inserted into the plant that encode toxins that target pests, along with their protein products.

31 The term "pesticide" includes "any substance or mixture of substances intended for use as a plant regulator." The term "plant regulator" includes a substance intended "through physiological action . . . for accelerating or retarding the rate of growth or rate of maturation, or for otherwise altering the behavior of plants or the produce thereof" (7 U.S.C. § 136).

32 In EPA's 1994 proposed rule, plant pesticides (now referred to as "plant-incorporated protectants") included narrowly-defined plant regulator substances that would act as a hormone to control growth, but excluded substances intended to alter the nutritional composition of the plant, to enhance resistance to herbicides, or to alter flavor or texture (EPA, 1994a).

33 "Chemical substance" is defined broadly to mean "any organic or inorganic substance of a particular molecular identity, including—(i) any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature and (ii) any element or uncombined radical" (15 U.S.C. § 2602).

Chapter 4: Regulating Microbial Products Engineered Using Synthetic Biology

In this chapter, we focus on the challenges and issues that may arise as microbial products engineered using synthetic biology become more common. Synthetic biology is expected to enable an unprecedented increase in the number and diversity of commercially available microbial products. This diversity is likely to include microbes with intended uses in the environment or in applications in which interaction with the environment is probable. While biotechnology development over the past twenty-five years has focused in large part on crop plants, product development using synthetic biology, particularly in the near-term, will likely focus on microbes.

While biotechnology development over the past twenty-five years has focused in large part on crop plants, product development using synthetic biology, particularly in the near-term, will likely focus on microbes.

To date, EPA's authorities under the Toxic Substances Control Act (TSCA) have been adequate to assess potential risks from genetically engineered microbes and to require appropriate risk mitigation measures. However, the anticipated influx of genetically engineered microbes for industrial use might stress EPA's resources and authorities, which could lead to regulatory delays or legal challenges. This challenge is detailed below along with policy options that could be pursued to address it.

The chapter concludes with three additional issues that, in our view, are worth tracking, but at this time do not require action. These include EPA's somewhat limited definition of "intergeneric microorganism" and two categories of genetically engineered microbes that are exempted or excluded from TSCA review.

4.1 Key Challenge

EPA may be constrained by inadequate funding and by the authority given to it under TSCA to address the anticipated influx of genetically engineered microbes for industrial use, which could lead to regulatory delays, inadequate review, and/or legal challenges.

EPA regulates genetically engineered microbes under TSCA.[34] With some exceptions, EPA regulates "intergeneric microorganisms," which it defines as microorganisms "formed by the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera" (EPA, 1997). In general, before initiating field trials of an intergeneric microorganism, a developer must get approval from EPA using a TSCA Experimental Release Application (TERA). Prior to using the microbe commercially, a developer must notify EPA through a Microbial Commercial Activities Notice (MCAN). Both the TERA and MCAN trigger time-limited review processes by EPA for potential health and environmental risks.

However, EPA's experience using this authority has been limited thus far. Since 1998,

34 EPA has exempted, by regulation, a number of low-risk genetically engineered microbes from the requirements for a Microbial Commercial Activities Notice (MCAN) or TSCA Experimental Release Application (TERA). These include microbes that are used in contained settings for research and development and microbes for commercial production purposes that use certain species as "recipient" microbes, that will be used in a contained structure with specified inactivation requirements, for which the genetic modifications are well-understood and are poorly mobilizable, and that are free of certain toxin DNA sequences (EPA, 2012b).

35 The EPA website lists 44 Microbial Commercial Activity Notices (MCANs) and 30 TSCA Experimental Release Applications (TERAs) (EPA, 2013a). Some of the MCAN submissions include multiple microbes while some TERAs represent different experimental releases for the same microbe. Also, while the TERA list is up to date, the MCAN list changes more frequently and so the website underestimates the total number.

approximately 75 engineered microbes have been submitted for review to EPA for testing or commercialization and have been evaluated under those authorities, including fewer than 30 for field testing in the environment.[35] Only a single genetically engineered microbe has been approved by EPA for commercial use in the environment.[36] Those small numbers can be contrasted with the thousands of release decisions made by APHIS in its field testing procedures for plants (APHIS, 2013a; Fernandez-Cornejo, et al., 2014), and the hundreds of biotechnology products that have been assessed by FDA in its regulation of drugs and vaccines (BIO, 2008).

This number should also be contrasted with the number of microbes that are likely to come into EPA for evaluation over the next few years. There are many applications of synthetic biology that are likely to yield commercial microbial products in that time frame, including some based on algae or other types of microbes with likely environmental interaction.[37] Some companies with large synthetic biology programs, including those producing algal biofuels, may consider dozens or even hundreds of variants of their microbial products during product development, each of which would require a TERA for field testing. According to EPA's TSCA Biotechnology Program website, EPA received 23 TERAs between 1998 and 2012. The agency received 7 in 2013 (EPA, 2013a).

Because it may see many more TERAs and MCANs than the agency has processed previously, it is not clear that new products would be given the same level of oversight that microbes have experienced to date. If EPA's TSCA Biotechnology Program is not given additional resources to keep pace with the anticipated workload, longer review times may become more common, thereby frustrating product developers. The broader diversity of microbes that synthetic biology will enable may also require EPA to employ a wider variety of specialized expertise, potentially exacerbating the problem.

The outcome of this likely scenario is hard to predict. It is possible that product developers would tolerate a longer regulatory process; EPA's current process is relatively efficient. EPA might be able to increase the size of its regulatory staff or increase its administrative efficiency. For example, as agency officials become more familiar with classes of microbes engineered using synthetic biology, the agency may be able to expand its exemptions to reduce the time that is spent on low-risk microbes and to better focus on those with more potential for environmental harm. EPA officials may also be able to develop a process for reviewing and approving MCANs and TERAs on a programmatic level where multiple, related notifications or applications (e.g. many variants of a single alga developed by a biofuel company) can be processed together.[38] These measures are also discussed in Option 1 below.

Some companies with large synthetic biology programs, including those producing algal biofuels, may consider dozens or even hundreds of variants of their microbial products during product development, each of which would require a TERA for field testing.

36 The microbe, a strain of *Sinorhizobium meliloti* used as an inoculant for alfalfa seeds for improved nitrogen fixation, was approved in 1997 (EPA, 2012c).

37 The Woodrow Wilson International Center for Scholars (Wilson Center, 2012) lists 38 applications that are likely to be covered by EPA.

38 For MCANs, it is not clear the extent to which this could be implemented: a similar procedure under TSCA for pre-manufacture notices for new chemicals (not microbes) is limited to six chemicals (EPA, 2013b) and MCANs thus far have been limited to six. For TERAs, the regulation states that "A person may submit a TERA for one or more microorganisms and one or more research and development activities, including a research program" (40 CFR § 725.250(c)). However, EPA has not issued guidance on how a program-level TERA should be pursued or would be evaluated.

Although such measures may be able to expedite product reviews, the number of applications and notifications to be submitted in the near and intermediate term may outpace any potential gains in efficiency. A less predictable outcome in this case may be for frustrated product developers to challenge EPA directly, suing to better define the extent of EPA's authorities over microbes under TSCA in the areas of uncertainty described below. Even absent legal challenges, EPA may come under pressure to more easily allow products to be field tested or commercialized.

While the agency's experience in regulating microbes has been limited, EPA officials believe that the agency has reasonably strong pre-market authorities to ask for data and information from product developers, both during the TERA process and when product developers move toward commercialization of their products by submitting MCANs.

In addition to a strain on resources, the number, diversity, and novelty of new microbes enabled by synthetic biology may create new challenges for EPA for its relatively untested pre-market authorities. There is some disagreement and uncertainty about how TSCA may function in this context. While the agency's experience in regulating microbes has been limited, EPA officials believe that the agency has reasonably strong pre-market authorities to ask for data and information from product developers, both during the TERA process and when product developers move toward commercialization of their products by submitting MCANs. The agency has worked with product developers to understand potential risks, to request information, and to develop the most appropriate tests and studies. Furthermore, it has the flexibility to ask questions that are most relevant to the particular product and that can address specific concerns for any potential adverse impacts.

EPA officials also believe that the agency has adequate authority to impose conditions on manufacture or use of engineered microbes to ensure their safe use through the use of Consent Orders[39] and "Significant New Use Rules."[40] While there have been few Consent Orders required in recent years for new intergeneric microbes, EPA officials used them frequently for early submissions (including for microbes submitted before rules for intergeneric microorganisms were finalized in 1997). The agency recently proposed a Significant New Use Rule relating to a genetically engineered strain of *Trichoderma reesei* used in the production of enzymes for ethanol production (EPA, 2012d). EPA officials were concerned that under some conditions of use, the microbe would not be contained to the appropriate level and has the potential to generate peptides with toxic characteristics; the proposed SNUR would allow EPA to evaluate a new intended use of the microbe and prohibit or limit that use if it may be hazardous. While this SNUR is not finalized, it demonstrates an important tool that EPA has available.

These pre-market tools under TSCA have been very important for the agency not only for regulating genetically engineered microbes, but also in its regulation of other (non-microbial) chemicals. For these more traditional chemicals, agency officials have found that product developers have been almost universally willing to agree to Consent Orders, if needed, or have withdrawn their submissions. While EPA's experience using TSCA for engi-

39 EPA can develop TSCA Section 5(e) Consent Orders in cases where a potential unreasonable risk is found. Such orders typically contain all or some of the following conditions: testing for toxicity or environmental fate once a certain production volume or time period is reached; use of worker personal protective equipment; New Chemical Exposure Limits (NCELs) for worker protection; hazard communication language; distribution and use restrictions; restrictions on releases to water air and land, and recordkeeping (EPA, 2013c).

40 Section 5(a)(2) of TSCA authorizes EPA to impose restrictions on "significant new uses" of chemical substances. In effect, Significant New Use Rules (SNURs) are a way for EPA to ensure that all manufacturers using a particular chemical substance follow the same rules to ensure its safe use (EPA 2013c).

neered microbes may be somewhat limited, the agency has seen thousands of applications for new chemical substances, and its successful experience with those non-microbial chemicals may indicate that TSCA, in practice, is a reasonably strong statute.

However, some legal experts have criticized TSCA as a weak regulatory law on a number of grounds (Kuzma, et al., 2009; Mandel, 2012; Marchant, 2012). In particular, questions have been raised whether TSCA gives EPA officials adequate authority to require tests (particularly ones that may be expensive but necessary), to place conditions on use, or to prevent the commercialization of a product.[41] While product developers may agree to Consent Orders (as discussed above), they are not legally required to do so. TSCA requires that once a manufacturer submits an MCAN, notifying EPA that it intends to commercially produce a new intergeneric microbe, EPA officials then have 90 days to make a finding. Some experts argue that if EPA would like to request more data or information, it must find that there is insufficient information to evaluate the human health and environmental effects of the substance, and either (1) that the microbe may present an unreasonable risk of injury to human health or the environment, or (2) that the microbe will be produced in substantial quantities and may be anticipated to enter the environment in substantial quantities or that there may be significant or substantial human exposure. This standard puts a substantial burden of proof on the agency

Questions have been raised whether TSCA gives EPA officials adequate authority to require tests, to place conditions on use, or to prevent the commercialization of a product.

Box E: Legal Uncertainty

Uncertainty about an agency's legal authority can arise in several ways. After Congress passes a law, agencies need to clarify how they will interpret and apply it, typically through regulations or guidance. Interested parties can and frequently do challenge the agency's implementing regulations, often on procedural or substantive grounds of exceeding the agency's authority. Uncertainty about legal authority can only be definitively settled when the issues have been raised and decided by the courts.

Even where there has been no immediate challenge to the law or the agency's rules, agency authority can still later be challenged in court as a defense to an enforcement proceeding or in response to an agency action. In the case of APHIS, for example, several lawsuits brought by advocacy organizations in the mid-2000s successfully challenged the authority of APHIS to grant partial deregulations of certain genetically engineered crops without conducting an environmental impact statement, despite the long standing of APHIS's regulations and procedures.

In writing regulations or taking enforcement actions, regulatory agencies frequently have to grapple with the practical question of how to balance questions of authority with the need to act, and the likelihood of successful legal challenge.

41 Some legal experts have also been critical of EPA's post-market authorities under TSCA. While companies are required to maintain records of allegations of harmful effects from their products, they are not required to monitor for such effects or report them to EPA unless they are specifically requested to do so. However, if the manufacturer obtains data indicating a "substantial risk" of injury to human health or the environment, it has a duty to report that information to EPA.

and may be particularly difficult for the agency to meet when it is faced with increasingly novel microbes. In the absence of this finding, a product can move to market after the 90-day evaluation period even without the additional data.

In the case of the TERA, which product developers must submit before beginning any field trials in the environment, EPA regulators have 60 days to review, put conditions on, and accept or deny the application. For both the TERA and the MCAN, the short time-frame allowed to EPA officials to make a determination has raised questions about the quality of review.

If provided adequate funding, EPA would likely be able to process the anticipated influx of engineered microbial products within its current authorities.

In practice, according to EPA officials, the law is more flexible than it appears. The 60 or 90-day periods have been used as negotiation periods during which EPA regulators and the product submitter reach agreement (including, potentially, the development of a Consent Order) on the practices that will be used by the manufacturer to minimize risks. Also, officials and product developers have "stopped the clock" to give product developers time to comply with requests for more tests. In general, when product developers have been unable to comply with those requests, they have withdrawn the application or notification.

While EPA officials believe that the agency's rule on genetically engineered microbes provides adequate tools for pre-market risk assessment, EPA's interpretation of TSCA's authority to assess and regulate the risks of these microbes has not been reviewed in any court challenge, thus some legal uncertainty remains. (See Box E on Legal Uncertainty.) These authorities may come under more scrutiny, particularly if product developers face longer delays, as described above.

4.2 Policy Options

Below, we present two options. The first is to simply wait and see, and increase resources to EPA if and when needed. Because the difficulties described above have not materialized yet, policy makers may choose to delay any changes until there is a clearer understanding of what pressures the agency will experience in the future. As needed, funding could be increased and efficiency measures pursued to allow EPA to maintain an effective program that functions largely the same as it does today, with an adequate amount of time spent with each product developer, and with regulatory officials confident that necessary tests are done. The second approach is to strengthen EPA's authorities under TSCA to increase the stringency of review and to give EPA more tools to ensure that each product receives appropriate oversight. It should be noted that these options are not mutually exclusive.

Option 1: If and when needed, provide additional funding for EPA's Biotechnology Program under TSCA and pursue efficiency measures to expedite reviews.

If and when the number of products increases beyond the ability of EPA officials to review them efficiently, additional funds could be directed to the program. This option would require either a process within EPA to prioritize funding for this program, or additional funding to be appropriated by Congress. In general, the agency has been able to allocate appropriate funding to TSCA's pre-market assessments as the number of notifications has changed over time. However, given the rapid increase in the number of notifications and applications and the diversity of the microbial products that synthetic biology is likely

to enable, extra vigilance may be required to anticipate funding needs.

If provided adequate funding, EPA would likely be able to process the anticipated influx of engineered microbial products within its current authorities and so avoid the type of delays, legal challenges, and pressures that are described in this chapter.

There are several ways that EPA officials could take steps to increase efficiency within existing authorities, including exempting low-risk microbes from MCAN or TERA requirements and developing procedures to assess and approve TERAs and MCANs on a programmatic level (i.e. for multiple microbes within a single submission). Such a program-level approach may be particularly important for TERAs, since product developers may want to test many variants of their engineered microbes experimentally before deciding which to pursue commercially. In some cases, a company may wish to test dozens or hundreds of variants in parallel; under the current system, the number of TERAs that would need to be prepared would be prohibitive for the company and, if submitted, would likely overwhelm EPA officials. For this reason, a program-level TERA process would be welcomed by the regulated industry and may ease pressure on the agency.

However, it may be difficult for EPA officials to implement these efficiency measures, particularly in the near-term, while maintaining confidence that each microbe receives the appropriate oversight. In the past, EPA has issued rules for exemptions as they have become familiar with particular species of microbes and those microbes have developed a history of safe use. It is not clear if and when EPA officials might gain the requisite experience and comfort with new types or applications of engineered microbes, which are likely to be more diverse and have more extensive modifications. A similar challenge may arise for the agency in developing rules or guidelines for program-level MCANs and TERAs. For TERAs in particular, where applications involve environmental release and where EPA has less experience, EPA officials may struggle to set parameters for a program of release of multiple engineered microbes that ensures that none pose an unreasonable risk, particularly for a program that includes a large number or a diverse set of microbes. Furthermore, the 60 or 90-day timeframes for EPA officials to complete evaluations (or to "stop the clock") would still apply to these program-level submissions.

During the 112th Congress, the Senate Committee on Environment and Public Works approved S. 847, a bill to strengthen TSCA, but it was not considered by the full Senate.

Option 2: Amend TSCA to strengthen EPA's ability to regulate intergeneric microbes.

This option envisions Congressional action. If and when Congress moves to amend TSCA, it could take measures to address some of the statutory weaknesses and uncertainties described above. Legislation to amend and strengthen TSCA is currently being considered in the Senate.[42] During the 112th Congress, the Senate Committee on Environment and Public Works approved S. 847, a bill to strengthen TSCA, but it was not considered by the full Senate (Library of Congress, 2013). A key provision in that bill was a requirement that developers of new chemical substances

42 The late Senator Frank Lautenberg and Senator David Vitter introduced S. 1009, the "Chemical Safety Improvement Act", on May 22, 2013, along with fifteen other co-sponsors; the bill has been referred to the Senate Committee on the Environment and Public Works. According to the bill's sponsors, it would enhance EPA's ability to regulate new chemicals and obtain needed health and safety information from chemical manufacturers (Lautenberg, 2013).

To date, product developers who use synthetic biology techniques have not questioned EPA's authority.

submit a minimum information set to EPA (Keller and Heckman LLP, 2012). It is not clear how this requirement would be implemented in the case of intergeneric microbes (living organisms are not mentioned in the bill), but such a provision could strengthen the ability of EPA officials in the TSCA Biotechnology Program to request necessary data. However, since living microbial products developed using synthetic biology are likely to be functionally diverse, EPA officials would need to maintain the flexibility to request a wide variety of data that may be relevant in order to perform broad risk assessments.

Congress could also consider several additional measures to strengthen EPA's authority, including:

- requiring product developers to demonstrate that there are no unreasonable adverse effects before a product can go to market (i.e., shifting the burden of proof from EPA to developers);
- extending the assessment periods for environmental release applications and for pre-market notifications to allow a more thorough assessment by EPA;
- instituting mandatory post-market reporting requirements; and/or
- reducing the burden of proof required for EPA to pursue post-market restrictions.

Such provisions could be applied to TSCA more generally or could be developed specifically for intergeneric microbes under TSCA.

This type of Congressional action would increase the authority that EPA brings to bear in regulating intergeneric microbes, thereby improving the ability of EPA officials to minimize risks. However, those in industry might argue that many of these options would increase the burden on product developers and thus may impede product development.

4.3 Additional Issues in the Regulation of Microbial Products

These "Additional Issues" were raised at the workshops we held and in other conversations over the course of our study, but in our view, do not currently represent major challenges to the regulatory system. As a result, we do not propose policy options at this point but note that these issues deserve to be periodically revisited as they each could develop into a more substantial challenge in the future. These issues include the regulatory treatment of microbes that are used for non-commercial purposes or that fall under other statutes and so are excluded from review under TSCA, as well as EPA's somewhat limited definition of "intergeneric microorganism." An interagency group under OSTP could be tasked to track these issues.

1. **Environmental release of non-commercial genetically engineered microbes may not receive appropriate oversight.**

TSCA requires pre-manufacturing notices only for the manufacturing and processing of new chemical substances for "commercial purposes" (15 U.S.C. § 2607(f)). EPA defines "commercial purpose" very broadly, but there may still be some environmental releases of a genetically engineered microbe that do not have a commercial purpose and would therefore not be covered under TSCA and EPA's regulations.[43]

This limitation has two potential implications. As discussed in the previous chapter, the NIH Guidelines prohibit covered researchers from releasing genetically engineered organisms outside of a contained area unless it is au-

thorized by a relevant regulatory agency.[44] If there is no agency with jurisdiction over the release, even legitimate research in the open environment has no way of being reviewed and allowed to proceed. As in the case with APHIS and plant developers conducting basic research discussed in Chapter 3, the lack of a relevant regulatory agency with jurisdiction over non-commercial genetically engineered microbes could hinder important basic research by preventing controlled field trials.

A second issue is that basic genetic engineering and synthetic biology tools are now being used by non-institutional experimenters. If these experimenters do not receive federal research funding, their work, even in contained laboratories, is not covered by the NIH Guidelines. Moreover, curiosity-driven experimentation in the open environment by do-it-yourself (DIY) researchers appears to be outside of EPA's authority to regulate.[45] Similarly, releases intended for purely educational or artistic purposes could also be outside EPA's purview.

This issue is not limited to synthetic biology, but the increased power of synthetic biology and the relatively low barriers to the use of the technology are likely to increase the number of people involved in such experimentation and provide them with more powerful genetic engineering tools. In the near-term, the relative simplicity and small number of microbes that can be engineered and released by such non-institutional researchers suggests that the probability of environmental harm is likely to be low, but there remains some concern that even a small release could result in an engineered microbe becoming established in the environment and having some health or adverse environmental effect. As the knowhow and technology of non-institutional experimenters becomes more sophisticated, this concern could increase, and public concerns could rise as well.

The lack of a relevant regulatory agency with jurisdiction over non-commercial genetically engineered microbes could hinder important basic research by preventing controlled field trials.

43 EPA presumes a commercial purpose for any research activity funded in whole or in part by a commercial entity, even if it is conducted at a university. Even when there is no commercial funding, activities are considered by EPA to be "commercial" if they are "conducted with the purpose of obtaining an immediate or eventual commercial advantage" (EPA, 1997). EPA's interpretation of these provisions is currently unclear. Some at EPA have argued that an environmental release of an intergeneric microbe would be considered commercial and therefore covered by TSCA if any research anywhere within the research institution gets commercial funding. This position could significantly expand the reach of EPA's regulations, but appear to go beyond what EPA's rules actually state. Furthermore, in finalizing its 1997 rule, EPA rejected an earlier proposal (EPA, 1994b) to consider all environmentally released microbes commercial. It also explicitly recognized a fundamental "academic nature" at universities that is not commercial (EPA, 1997).

44 Under NIH Guidelines, researchers may not release genetically engineered organisms into non-contained environments except under the approval process of a relevant federal regulatory agency. If there is no relevant federal regulatory agency, as would be the case for genetically engineered microbes developed for a non-commercial purpose, no release can be made without violating NIH Guidelines.

45 Many DIY biologists, including those working in community labs, such as Genspace in Brooklyn, NY (http://genspace.org/page/about), and BioCurious in the San Francisco Bay Area (http://biocurious.org/about/), explicitly pursue commercial applications for their engineered microbes, making much of the research in these settings subject to EPA oversight. Because these facilities practice and document basic biosafety procedures, their contained research is likely exempt from MCAN requirements based on safe-use exemptions. As would be the case for any other commercial endeavor, any environmental release of a microbe with commercial intent would require a TERA. A barrier to compliance for these groups, and particularly for DIY biologists practicing outside of a community lab, is knowledge of EPA procedures.

In the near-term, the relative simplicity and small number of microbes that can be engineered and released by non-institutional researchers suggests that the probability of environmental harm is likely to be low.

2. There may be an increase in the number of genetically engineered microbial products that are excluded from TSCA and do not undergo pre-market review under other authorities.

TSCA excludes substances (including by extension genetically engineered microbes) that fall under the purview of other statutes, including food, dietary supplements and cosmetics (covered by FDA under the Food, Drug, and Cosmetic Act [FDCA]) (40 C.F.R. § 720.3).[46] As noted in Chapter 2, how such microbial products are regulated, whether genetically engineered or not, depends on the specific law governing the intended use of the product. Policy makers have determined that some products should be subject to a mandatory pre-market approval process, while other products can be sold without prior review but are subject to agency action if there is evidence of harm once on the market. If a genetically engineered microbial food product (e.g., a living microbe used as a probiotic in yogurt) is considered a food additive, it will go through a rigorous pre-market review, including an environmental assessment for NEPA.[47] If it is not, it could go through FDA's voluntary consultation process for food or straight to market without a consultation.[48] Engineered microbes that are used to produce dietary supplements and cosmetics are subject only to post-market action if they cause harm to human or animal health.[49] (See Figure 1.)

The application of synthetic biology to such microbial products does not necessarily raise new regulatory issues for health and safety. However, without pre-market review, some microbial products could be tested and produced at commercial scales without any assessment of potential risks to the environment. Most microbes engineered using synthetic biology are likely to be grown in enclosed bioreactors, but some products, particularly engineered algae (e.g., for the production of vitamin D, a dietary supplement), will necessarily have some interaction with the environment.[50] As discussed in Chapter 2 (and indicated in Figure 1), FDA officials have limited authority to consider environmental harm that does not directly threaten the health of humans or animals in making regulatory decisions, including post-market decisions to place limitations on the sale of a product. This is an area in which a challenge

46 Also excluded are pesticides, drugs, tobacco and tobacco products, nuclear materials, and firearms.

47 It is not clear whether a new genetically engineered microbe that produces an already-approved food additive would undergo any mandatory pre-market review if the end product food additive is for the same use and is of a similar quality.

48 If a genetically engineered microbe is "generally recognized as safe" (GRAS) under conditions of its intended use, it is not considered a food additive. Developers may voluntarily notify FDA of its determination that a substance is GRAS, but are not required to do so. As noted in Chapter 2, NEPA assessment is triggered by federal action. A food additive approval from FDA would require a NEPA assessment and so a broad range of potential environmental impacts would be assessed. The voluntary process is not considered a federal action, and so there would be no NEPA assessment. See also footnote 11.

49 There is no pre-market assessment process for cosmetics. For new dietary ingredients (NDI's), a product developer must submit a notification to FDA describing the new ingredient and containing information supporting a claim that the product is reasonably expected to be safe. If FDA foresees any potential harm, it can issue a letter to the product developer detailing its concern; such a letter, while not having regulatory authority, can be very effective at ensuring that products are safe. However, this notification requirement would not apply to new methods of producing already listed dietary ingredients (e.g., using a new strain of algae to produce vitamin D). Also, this notification process is not considered a federal action and so does not trigger environmental assessments under NEPA.

for the regulatory system may arise due to the scope and number of genetically engineered microbes that synthetic biology may enable, their potential for interaction with the environment, and, perhaps as importantly, the public perception of such products.

3. EPA's definition of "intergeneric microorganism" may not be adequate to cover microbes engineered using synthetic biology.

EPA regulates only those engineered microorganisms that are "intergeneric."[51] EPA chose this standard to avoid regulating microbial variants that may arise naturally (i.e., microbes that may have exchanged DNA with closely related species), to best capture potential novel traits, and to give the agency an enforceable and limited metric. However, there has been discussion of whether the definition of "intergeneric microorganism" would include chemically synthesized genetic sequences (Rodemeyer, 2009). EPA's final rule issued in 1997 defined "intergeneric" only in terms of DNA isolated from organisms of different genera. To clarify its intent, EPA recently updated its online summary of regulations to indicate that a synthesized gene that is different or not known to have an identical sequence to one that occurs in the same genus as the host organism would also be considered "intergeneric"[52] (EPA, 2012b). Although EPA has not amended its rules, its interpretation would likely be given deference by a court if it were challenged. To date, product developers who use synthetic biology techniques anticipate regulation by EPA, and have not questioned this authority.

50 As noted in footnote 15, FDA has the authority to oversee the manufacturing process of dietary supplements to ensure quality and safety through Good Manufacturing Practices, which could have the indirect effect of preventing unwanted environmental exposures.

51 EPA defines "intergeneric" microorganisms as "microorganism[s] that [are] formed by the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera. (1) The term intergeneric microorganism includes a microorganism which contains a mobile genetic element which was first identified in a microorganism in a genus different from the recipient microorganism. (2) The term intergeneric microorganism does not include a microorganism which contains introduced genetic material consisting of only well-characterized, non-coding regulatory regions from another genus." (40 C.F.R. § 725.3)

52 While EPA's 1997 final rule does not specifically address chemically synthesized genes, EPA's 1986 Policy Statement under the Coordinated Framework indicated that a chemically synthesized gene would be considered "intrageneric" if it is "identical" to one occurring in the same genus as the host organism (EPA, 1986). EPA's current interpretation as indicated on its web site is consistent with this earlier statement.

Acknowledgements

We would like to thank the U.S. Department of Energy and the Alfred P. Sloan Foundation for funding this project. Throughout this process, we depended greatly on input from a wide variety of people whose combined expertise greatly exceeded that of our own. Those listed below provided their time and perspectives in workshops, discussions, and/or reviews of our early manuscripts. The authors of our commissioned papers, Tom Bundy, Gary Marchant, Greg Mandel, and Jordan Paradise and Ethan Fitzpatrick, provided important context early on in the process. Sean Valle, our JCVI intern for summer, 2012, helped with preparations for the workshop in August, 2012.

Workshop participants and observers, reviewers of drafts, and others who contributed to this report:

- Ryan Bayha, Office of Biotechnology Activities, National Institutes of Health
- Jason Bobe, Personal Genomes and DIYBio.org
- Tom Bundy, formerly U.S. Department of Agriculture
- Alice Chen, Keller and Heckman LLP
- Jacqueline Corrigan-Curay, Office of Biotechnology Activities, National Institutes of Health
- Genya Dana, AAAS Fellow, U.S. State Department of State
- Fred Degnan, King & Spalding
- Dan Drell, Biological and Environmental Research, Department of Energy
- Susan Ehrlich, former judge and member, National Science Advisory Board for Biosecurity
- Adam Finkel, University of Pennsylvania
- Kevin Finneran, National Academies Committee on Science, Engineering, and Public Policy
- Ethan Fitzpatrick, Seton Hall University
- John Glass, J. Craig Venter Institute
- Theresa Good, National Science Foundation
- Jaydee Hanson, International Center for Technology Assessment
- Eric Hoffman, Friends of the Earth
- Alicia Jackson, Defense Advanced Research Projects Agency
- Peter Jutro, Environmental Protection Agency
- Kristin Kaplan, Food and Drug Administration
- Todd Kuiken, Woodrow Wilson International Center for Scholars
- Jennifer Kuzma, University of Minnesota
- Rachel Levinson, Arizona State University
- Gregory Mandel, Temple University
- Gary Marchant, Arizona State University
- Martha Marrapese, Keller and Heckman LLP

- Sally McCammon, Animal and Plant Health Inspection Service, U.S. Department of Agriculture
- Gwendolyn McClung, Environmental Protection Agency
- Alan McHughen, White House Office of Science and Technology Policy
- Margaret Mellon, Union of Concerned Scientists
- Elizabeth Milewski, Environmental Protection Agency
- Paula Olsiewski, Alfred P. Sloan Foundation
- Jordan Paradise, Seton Hall University
- Ari Patrinos, Synthetic Genomics, Inc.
- Eleonore Pauwels, Woodrow Wilson International Center for Scholars
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- Carlos Peña, White House Office of Science and Technology Policy
- Pablo Rabinowicz, Biological and Environmental Research, U.S. Department of Energy
- Kent Redford, Archipelago Consulting
- Larisa Rudenko, Food and Drug Administration
- Mark Segal, Environmental Protection Agency
- Rina Singh, Biotechnology Industry Organization
- Jessica Tucker, Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services
- Sean Valle, Stanford University and intern at the J. Craig Venter Institute
- Elizabeth White, Biological and Environmental Research, U.S. Department of Energy
- Malini Wileman, Food and Drug Administration
- Joyce Yang, Office of Energy Efficiency and Renewable Energy, U.S. Department of Energy.
- The Biotechnology Industry Organization's Synthetic Biology Working Group

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Appendix

Legal Authority for Regulating Biotechnology Products under the Coordinated Framework

For a summary table of legal authorities that have been applied to genetically engineered products, see Figure 2 at the end of this Appendix.

USDA-APHIS

Plant pests. USDA's Animal and Plant Health Inspection Service (APHIS) has broad regulatory authority to control the importation, interstate movement, and introduction of plant and animal pests and diseases under a number of laws (Plant Protection Act, 7 U.S.C. § 7758(c); Animal Health Protection Act, 7 U.S.C. §§8303 *et seq.*). APHIS has issued regulations[53] applying this authority to certain genetically engineered organisms for which the donor or recipient organism, or the vector or vector agent, is classified as a plant pest. Since plant genetic engineering has often required the use of a plant bacterium such as *Agrobacterium tumefaciens* to transfer the desired DNA into the plant's genome, this definition has captured many genetically engineered plants, including food crops, plants engineered to produce industrial or pharmaceutical chemicals, or plants with other desirable agronomic traits.

Prior to field trials or other environmental releases of covered genetically engineered organisms, developers are required by APHIS either to notify the agency (in the case of certain low-risk and familiar organisms) or to apply for a field trial permit. To grant a permit, APHIS reviews submitted protocols from the developer to determine whether the plant can be released into the environment without posing a plant pest risk and to place necessary conditions on use to mitigate any plant pest risk. In addition, under the National Environmental Policy Act (NEPA) (42 U.S.C. § 4321 *et seq.*), APHIS must also separately conduct an environmental assessment on whether or not the permit, if granted, would have a "significant impact on the environment." If it would, APHIS would be required to conduct an Environmental Impact Statement (EIS). (See more on NEPA below.)

Following field trials, developers who want to take the genetically engineered plant into commercial production typically petition APHIS for a determination of "non-regulated status," which in essence is a finding by the agency that the plant does not pose a plant pest risk and that it therefore has no further regulatory interest in the plant.

EPA

Genetically Engineered Microorganisms. The Toxic Substances Control Act (TSCA) (15 U.S.C. §2601) gives EPA various authorities to regulate toxic chemicals. It excludes certain categories, including food, drugs, pesticides, tobacco, cosmetics, food additives, and medical devices (15 U.S.C. § 2602(2)(B)). Section 5 of TSCA gives EPA the power to screen and track new chemical products before they come to market. Manufacturers are required to give EPA notice prior to producing a new chemical substance, defined as a substance not already on EPA's list of existing chemicals. TSCA also requires manufacturers to give EPA information that it has or might "reasonably ascertain" relating to the potential health or environmental impacts of the new chemical substance. EPA then reviews the notification and determines whether it "presents or will present an unreasonable risk." If an existing chemical has a significant new use, EPA may also issue restrictions through a "significant new use rule" (SNUR).

EPA has taken the position that new, non-naturally occurring arrangements of DNA constitute new chemical substances under TSCA and has issued rules applying the Section 5 notification provisions to developers of certain "intergeneric microorganisms," defined as a "microorganism that is formed by the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera" (EPA, 1997). In its rule, EPA created a customized pre-production notification process for covered intergeneric micro-

53 7 C.F.R. Part 340. The full definition of a "regulated article" states: "Any organism which has been altered or produced through genetic engineering, if the donor organism, recipient organism, or vector or vector agent belongs to any genera or taxa designated in §340.2 and meets the definition of plant pest, or is an unclassified organism and/or an organism whose classification is unknown, or any other organism or product altered or produced through genetic engineering which the Administrator determines is a plant pest or has reason to believe is a plant pest."

organisms called the Microbial Commercial Activity Notice (MCAN). EPA's rules also require developers to notify EPA prior to testing any genetically engineered microorganisms outside of a contained environment when the organism will be used for a commercial purpose.

Pesticides. EPA also regulates biotechnology products intended for use as pesticides under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) (7 U.S.C. §136 *et seq.*). Before a pesticide can be marketed, it must be approved by EPA with the finding that the pesticide, when used as instructed, will not "generally cause unreasonable adverse effects on the environment." Pesticides can be tested in field trials under an experimental use permit; certain small-scale (fewer than 10 acres) field trials are exempted.

Under its FIFRA authority, EPA has issued specific rules that apply to genetically engineered microorganisms intended for use as pesticides under which developers must notify EPA prior to any field trial in an uncontained environment (EPA, 1994c). In addition, EPA has issued regulations applying to the pesticides expressed in certain varieties of genetically engineered plants, so called "plant-incorporated protectants" (EPA, 2001).

FDA

Food and Food Additives. The Food, Drug and Cosmetic Act (FDCA, 21 U.S.C. §301 *et seq.*) is one of the oldest regulatory statutes, originally passed more than 100 years ago to deal with the "adulteration" of foods. Under the FDCA, novel whole foods do not require FDA pre-market review for safety. Instead, FDA's food safety authority is an example of a "post-market" regulatory system, under which FDA can step in to take action when there is evidence that a food substance is causing harm.

Food additives, on the other hand, must be approved by FDA as safe before they can be used in food. Food additives are substances like preservatives or colors intended to be added to food so that it is a component of the food or affects the characteristics of a food. However, substances that are "generally recognized as safe (GRAS)," such as seasonings, are not considered food additives and do not require prior FDA review for safety.

In 1992, FDA issued a policy statement in which it indicated that if a genetically engineered food was "substantially equivalent" to food made in a conventional manner, it would presume that the genetically engineered food was "as safe as" the conventional food and would require no pre-market scrutiny (FDA, 1992). FDA also stated that substances added to the food by the engineering process were presumed to be "generally recognized as safe." While FDA has left open the door to use its authority under the food additive provisions of the Act in the event that a food from a genetically engineered crop is not substantially equivalent or contains substances that cannot be presumed to be GRAS, in practice, FDA has not used that authority.[54] FDA encourages developers of foods derived from genetically engineered crops to meet with FDA officials for informal consultations before marketing their products.

Dietary Supplements. The FDCA also gives FDA limited oversight authority over dietary supplements like vitamins and herbs. Dietary supplements are defined in the Act as a product "intended to supplement the diet" and containing one or more "dietary ingredients" such as vitamins, herbs, and substances found in the diet. Dietary supplements are not subject to pre-market approval for safety; instead, manufacturers are responsible for ensuring that the product does not pose unreasonable risks of illness or injury. FDA must be notified of new dietary ingredients (NDI) 75 days prior to their sale, and manufacturers are required to provide evidence along with the NDI notification that the supplement will be "reasonably expected to be safe"; however, FDA does not approve the NDI or make a finding that it is safe. In addition, manufacturers must report serious adverse effects. FDA may take steps to remove dietary supplements from the market but bears the burden to show that such products are unsafe.

Human Drugs, Biologics, and Medical Devices. The FDCA and the Public Health Service Act (42 U.S.C. § 201 *et seq.*) provides FDA with authority to regulate the safety and efficacy of human drugs, biologics, and medical devices. These

54 One exception is the case of the Flavr-Savr tomato, the developer of which voluntarily requested an approval of an antibiotic resistance marker gene as a food additive in 1991. FDA approved the use of the marker gene as a food additive in 1994.

products are subject to a mandatory pre-market approval requirement; they may not be sold unless FDA has found that the drugs, biologics, or medical devices are safe and effective. FDA regulates the use of these products through label requirements indicating procedures for their safe use, and requires manufacturers to report serious adverse events once the products are on the market. Post-market, FDA has the authority to withdraw an approved application in light of new evidence demonstrating safety risks. In addition to approving the drug or biologic, FDA also oversees the manufacturing process to ensure the safety, purity, and effectiveness of the product. FDA therefore has oversight over the use of genetically engineered bacteria in confined bioreactors used to make human drugs and biologics, as well as the use of genetically engineered animals to produce human drugs or biologics (FDA, 1995). Similarly, FDA would have oversight over the manufacturing process for human therapeutics derived from genetically engineered crops (FDA, 2002).

Animal Drugs. The FDCA defines a drug in part as any article intended to "affect the structure or function of the body of man or animal" (21 U.S.C. §321(g)(1)(C)). Unless an intended animal drug is generally recognized as safe and effective, it is considered a "new" animal drug and therefore may not be marketed without a FDA-approved new animal drug application. In considering safety, FDA takes into account not only that the drug is safe for the animal, but in the case of a food-producing animal, the safety of the food to eat. Developers must notify FDA before conducting any experimentation of the drug on an investigational animal (21 C.F.R. Part 511).

In 2009, FDA issued final guidance indicating its intent to regulate genetically engineered animals under its new animal drug approval authority. FDA takes the position that the genetic construct and its expressed proteins are new animal drugs for the purposes of the FDCA (FDA, 2009).

Cosmetics. FDA has limited authority over cosmetics, defined generally as articles intended to be applied to the human body for beautification purposes. (As with many products covered by FDA, how a product is marketed and what claims are made for its use determine to a significant extent how it is regulated.) FDA's authorities in this area are post-market in nature and have been used only rarely. Cosmetics are largely left to voluntary self-regulation by the cosmetic industry.

NIH

NIH administers the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) to ensure that laboratory research is done under conditions of containment appropriate to ensure safety. The NIH Guidelines were amended and retitled in March, 2013, to clarify that synthetic techniques raising similar safety issues would also be covered (NIH, 2012; NIH, 2013). The NIH Guidelines apply to rDNA or synthetic nucleic acid research funded by the National Institutes of Health and many other government research funding agencies. The NIH Guidelines are a term and condition of grant awards for institutions that receive NIH (or other federal) funding for rDNA or synthetic nucleic acid research; if they fail to comply with the Guidelines, they risk losing their funding.

While the NIH Recombinant DNA Advisory Committee (RAC) initially reviewed most biotechnology research proposals in the 1970s, over time the RAC has delegated much of its review authority for rDNA and synthetic nucleic acid research to local Institutional Biosafety Committees (IBCs). Under the NIH Guidelines, each research institution receiving NIH funding for applicable research is required to establish an IBC to review and approve these experiments for compliance with the Guidelines. The IBC includes a range of expertise appropriate to the proposed research. Depending on the research being proposed, the investigator may need to get IBC approval prior to beginning her or his research. NIH partners with institutions to ensure that IBCs understand the NIH Guidelines and are working effectively.

Research institutions that do not receive any NIH or other federal funding for rDNA or synthetic nucleic acid research are not required to follow the NIH Guidelines. Neverthe-

less, many entities follow the Guidelines voluntarily because they provide a set of "best biosafety practices" that define a de facto standard for research institutions not covered. Institutions that fail to follow practices such as those in the NIH Guidelines could be found liable for negligence in the event of an adverse safety incident.

NIH Guidelines apply only to contained laboratory research and do not cover research on genetically engineered organisms in the open environment. Unless the release has been authorized by a federal agency with appropriate jurisdiction, a researcher receiving NIH or other federal funding for rDNA or synthetic nucleic acid research would violate the Guidelines by conducting research in the open environment.

NEPA

Regulatory agencies must also comply with numerous other acts that may influence the process under which they exercise their regulatory authorities. While not a formal part of the Coordinated Framework for the Regulation of Biotechnology, the National Environmental Policy Act (NEPA) is a particularly important procedural law with respect to the regulation of genetically engineered organisms (42 U.S.C. 4321 *et seq.).* NEPA requires agencies to develop a detailed Environmental Impact Statement (EIS) for any major action that has a significant impact on the environment.[55] As a result, agencies must initially assess whether actions such as granting permits would have a "significant" environmental impact; if an agency finds that the action would not have a significant impact, it must issue a finding to that effect. The environmental assessment process requires the agencies to consider environmental risks beyond those for which they are responsible for directly regulating and provides the public with important information about environmental impacts of the proposed action. While NEPA provides no additional legal authority on which the agency can make its regulatory decision, as a practical matter, product developers have an incentive to mitigate their environmental impacts to avoid the cost and delay of a full EIS. Agencies also frequently exempt certain categories of actions from the requirement to conduct an environmental assessment on the grounds that such actions are unlikely to have significant environmental impacts.

55 In general, EPA regulatory reviews are considered to be equivalent to NEPA assessments and so EPA actions are exempted from NEPA.

Figure 2: Summary Table of Legal Authorities for Regulating Products of Genetic Engineering

Agency	Legal Authority	General scope of law – Products or Actions Covered	Applied to Products of Genetic Engineering
USDA	Plant Protection Act	Import, interstate transportation or introduction of plant diseases and pests.	Plants genetically engineered if plant pest used as donor or recipient organism or vector or vector agent.
EPA	Toxic Substances Control Act, §5	"New" chemical substances.	Microorganisms containing combination of genetic material from different genera ("intergeneric microorganisms"); does not include food, drugs, pesticides or other products regulated elsewhere; specified "low-risk" microorganisms in containment are exempted.
EPA	Federal Insecticide, Fungicide, and Rodenticide Act	Substances intended for killing or controlling pests; certain low-risk pesticides exempted.	Genetically engineered microorganisms intended for use as pesticides; pesticides expressed by genetically engineered plants.
FDA	Food and feed (Food, Drug, & Cosmetic Act)	Substances intended for use as human food or animal feed.	Food and feed derived from genetically engineered crops if substantially equivalent to conventional food; otherwise may be a food additive.
FDA	Human and animal drugs (Food, Drug, & Cosmetic Act; Public Health Service Act)	Substances intended to alter the function or structure of humans or animals.	Human and animal drugs produced by genetically engineered bacteria or animals, or containing genetically engineered organisms; gene products in animals engineered with heritable traits.
FDA	Food Additive (Food, Drug, & Cosmetic Act)	Substances that are a component of food or affect a characteristic of food and are not Generally Recognized as Safe (GRAS).	Incidental genetic materials added by genetic engineering of whole foods are presumed to be GRAS, but could be considered food additives if not usually found in food; also covers food additives created by or containing genetically engineered organisms.
FDA	Dietary Supplements (Food, Drug, & Cosmetic Act)	Substances that are not food additives used as dietary supplements (vitamins, herbs, etc.).	Dietary supplements derived from or containing genetically engineered organisms.
FDA	Cosmetics (Food, Drug, & Cosmetic Act)	Substances used as cosmetics (applied to body for beautifying).	Cosmetics derived from or containing genetically engineered organisms.
NIH	Condition of research grant	All research involving recombinant or synthetic DNA at any institution that receives NIH (or other federal) funding for such research; all researchers receiving such funding.	Research for biotechnology products that meet the funding conditions.
All agencies (excludes EPA laws)	National Environmental Policy Act (NEPA)	Significant federal actions (such as permits or product approvals).	Agency actions (including permits and approvals) involving genetically engineered products that could have significant impact on environment.

	Covered Risk Issues	Risk Assessment Authority	Risk Management Authority
	Impacts on plants and animals from diseases and pests.	USDA reviews notifications and conducts risk assessments on data provided by developer to issue permits for field trials; conducts additional assessment when developer petitions for non-regulated status.	Imposes conditions on field trials through notification and permits; if no plant pest risk, product is de-regulated.
	Human health and safety and environmental concerns.	EPA conducts pre-market risk assessment for environmental release (TERA) or manufacture (MCAN) based on information developer has or can reasonably obtain.	Environmental release of covered intergeneric microorganisms must be approved by EPA; developers must notify EPA prior to manufacturing intergeneric microorganisms for commercial use; EPA can negotiate conditions for safe use through Consent Orders and impose similar restrictions on other manufacturers through Significant New Use Rules (SNURs).
	Human health and safety and environmental concerns.	EPA conducts risk assessment based on data from tests it requires of pesticide developers for small-scale field trials and for wide sale and distribution.	Requires EPA pre-market approval; requires monitoring and adverse event reporting; EPA imposes conditions of safe use through labeling; approves permits for small-scale non-contained field trials.
	Human and animal safety.	Developers may voluntarily share information with FDA pre-market; FDA makes no finding.	No pre-market approval. FDA may act to take product off market if evidence of harmful effects to humans or animals.
	Human and animal safety, including safety of food from food animals; effectiveness of drugs; for animal drugs, includes environmental hazards affecting health of humans and animals.	FDA assesses efficacy and safety of human and animal drugs based on data (often clinical trials) provided by developer.	Requires FDA finding of safety and efficacy for intended purposes before product can be marketed.
	Human safety; includes environmental hazards affecting health of humans and animals.	FDA assesses data provided by manufacturer to show food additive presents "reasonable certainty of no harm."	Requires FDA finding of "reasonable certainty of no harm" before food additive can be marketed.
	Human safety.	For new dietary ingredients, developers must send a notification to FDA; FDA makes no finding.	No pre-market approval. FDA may act to take product off market if evidence of harm to humans.
	Human safety.	No premarket review is undertaken; FDA makes no finding.	No pre-market approval. FDA may act to take product off market if evidence of harm to humans.
	Biosafety: safety of lab workers as well as surrounding communities.	Requires investigator and research institution to assess risk of research involving recombinant or synthetic DNA; requires notification to or approval from the research institutional biosafety committee.	Relies on investigator or research institution's risk assessment to follow the guidelines that define appropriate physical or biological containment to ensure safety given the risk of the research.
	Broad environmental and human health impacts.	Agencies required to conduct an environmental assessment of proposed agency action to determine if "significant impact"; if yes, must conduct more thorough environmental impact statement.	Only requires analysis. Developer may voluntarily mitigate risks to avoid "significant impact" finding. No substantive authority to deny agency action.

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