THE DNA OF THE U.S. REGULATORY SYSTEM:

ARE WE GETTING IT RIGHT FOR SYNTHETIC BIOLOGY?

October 2015

Synthetic BIOLOGY PROJECT

Wilson Center

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THE DNA OF THE U.S. REGULATORY SYSTEM:

Are We Getting It Right for Synthetic Biology?

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EXECUTIVE SUMMARY

Recommendations

U.S. regulatory oversight of synthetic biology across the board needs to be modernized to reflect and address the promising technologies routinely entering the market. From a statutory perspective, the pertinent laws appear sufficiently broad to empower federal agencies to address potential risks and promote the potential benefits of synthetic biology. The regulatory infrastructure, however, is ill-suited to address all the regulatory implications of new products derived from synthetic biology.

Improvements that are urgently needed include:

- Increased funding to federal agencies, including "embedded" new technology stewards in each office of all relevant federal agencies to monitor and coordinate topics of emerging technologies and share information with other agency offices
- Dedicated centers of technological excellence in pertinent federal offices to stay abreast of new developments
- Regular routine intervention by industry and academic innovators to brief government agencies on trends, developments, and challenges
- Implementation of an ongoing process to demystify synthetic biology and its products so that they are more clearly and accurately understood by federal decision-makers and the public
- Developing a long-range, government-wide strategy to assure that, going forward, the regulation of synthetic biology encourages innovation while timely identifying and addressing risks through a science-based, transparent process that encourages public confidence

Some of these recommendations are reflected in a July 2, 2015, memorandum issued by the White House Office of Science and Technology Policy that directs the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and the Department of Agriculture (USDA) to update the 1986 Coordinated Framework for Regulation of Biotechnology, under which these agencies have proceeded for nearly three decades. The directive to revise the Coordinated Framework is long overdue. Developments in synthetic biology will not halt during the overhaul of the Coordinated Framework. Improvements in regulatory oversight can and should be put into place, even while the updating of the Coordinated Framework is in progress.

Report Summary

As highlighted in this report, especially in the illustrative case studies, competing and sometimes conflicting jurisdictional issues confound, if not frustrate, prompt and effective government oversight of synthetic biology. The novelty of some technologies challenges even government staff in sorting out which agency has primary jurisdiction over a particular product or new technology or which office within an agency should be exercising regulatory oversight.

The Oxitec case study highlights the threshold regulatory issues that can arise within a single agency – in this case, the FDA -- in the synthetic biology context. Oxitec has developed a genetically engineered mosquito that is highly effective in decreasing the population of disease-carrying *A. aegypti* mosquitos through breeding after the engineered mosquito is released into the wild. But the Oxitec mosquito does not fit cleanly into any FDA regulatory category; eventually it was determined to assess it as an animal drug by one office of the FDA rather than by another FDA office as a human drug though its ultimate goal is to reduce yellow fever and allied diseases in human beings -- and hence to act as a human drug. Uncertainty is expensive. Without a reliably defined regulatory assessment pathway, innovation is discouraged. For Oxitec, a threshold question even had arisen whether the USDA, rather than FDA, should be in charge if the engineered mosquito could be described as a pest control technology.

Where the synthetic biology product is a cosmetic ingredient, uncertainties are magnified because cosmetics, in most cases, are not subject to pre-market review by FDA, which typically relies on enforcement authorities it can deploy against improperly labeled cosmetics already on the market. Accuracy in labeling is a slippery slope when it comes to synthetic biology, as described in the case study on squalene, an emollient in lotions. The best source of natural squalene is shark oil, but with some shark species deemed endangered and plant sources often uneconomical, the biotechnology firm Amyris has developed and is marketing synthetic squalene, apparently through the engineering of proprietary yeast strains, for cosmetic use. This poses the question whether synthetically derived squalene is the same for regulatory/labeling purposes as squalene from fish oil or plant oil sources. Consumers are entitled to accuracy in labeling, but neither consumers nor product developers are well served if the regulatory agency in charge has not addressed and clarified the issue ahead of the launch of the cosmetic product in the commercial market.

The fundamental issue of which regulatory statute applies to a synthetic biology product can be unexpectedly complex, as depicted by the PBAN case study. PBAN is a naturally occurring substance that encourages female insects to produce pheromones to attract males for mating; researchers have developed a genetically modified strain of *E. coli* that yields a synthetic PBAN used in an innovative process for moth control. Mixed with a sugar solution, the synthetic PBAN is placed in a trap as food for female moths, inducing them to produce pheromones, which in turn attracts male moths into the trap. The use of a biopesticide in a trap for purposes of mitigating a pest typically requires registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), despite a FIFRA exemption for pheromones; synthetic PBAN, while inducing pheromone production, is not itself a pheromone. Thus PBAN is subject to FIFRA although it is a more benign approach to pest control than is a conventional pesticide. As the case study notes, if synthetic PBAN had obtained the benefit of the FIFRA exemption, it still might be subject to the Toxic Substances Control Act (TSCA) or other authorities. Depending on its use, and on whether other substances would be placed in the trap along with it, other regulatory scenarios could be triggered. The process of deciding whether and how to regulate a synthetic biology product may well require as

much effort as the regulatory process itself.

In some instances, synthetic biology products go without regulatory oversight because the relevant statute, as read by the implementing agency, does not cover them. The Plant Protection Act (PPA) extends only to "plant pests," a defined term that USDA's Animal and Plant Health Inspection Service (APHIS), in a reading affirmed by a federal appeals court, construes the term to exclude genetically engineered plants from regulation unless the plants themselves, the genetic material, or the engineering method involve plant pests. For this reason, APHIS declined to take jurisdiction over either "BioGlow" or the "Glowing Plant" as the case study illustrates. The former now commercialized and the latter, an open-source technology funded through a Kickstarter campaign. Seeds of the glowing plant were made available to consumers as supporter bonuses and in Do-It-Yourself (DIY) kits where individuals can make the genetic transformation themselves. Synthetic biology was far in the future when the original legislation that became the PPA was enacted – and it shows.

Not only is the underlying legislation often ill-equipped to address the challenge of commercialized synthetic biology, the problem is exacerbated at the implementing agency level. Given the extreme and growing shortages in government staff and funding throughout the federal agencies, including those whose regulatory reach extends to synthetic biology, technological literacy remains a critical problem. Government personnel with institutional know-how and expertise are retiring from the workforce and not always being replaced, and those who are added are not being provided with opportunities to understand fully new synthetic biology technologies entering the commercial space. In addition to the recommendations outlined above, better, more systematic, and routine communication and coordination between and among federal agencies is also urgently needed. The deeply-embedded stove piping confounds communication and coordination within and among government offices and blunts opportunities for more efficient, informed reviews of new products moving to market.

INTRODUCTION

Biology focuses on cells as basic life units, and genes as basic units of code that define heredity. Scientists long ago mastered engineering genes to functionalize desirable traits and removing genes from one organism and inserting them into another organism to achieve a specific intended scientific or commercial purpose. While there are many definitions of synthetic biology, key to each are the notions of scope and speed. While the underlying principles of synthetic biology are the same as those from traditional recombinant DNA (rDNA) techniques, what is different about synthetic biology, and important from a governance perspective, is the scope and speed of genetic change that synthetic biology can achieve. The application of standardized engineering techniques to biology can kick-start quickly and relatively inexpensively the creation of organisms and entire biological systems with novel or specialized functionalities, and these techniques are widely accessible to both institutional and non-institutional stakeholders, including the citizen science community.

This report discusses synthetic biology, reviews the U.S. regulatory system that governs products of synthetic biology and assesses whether this system is effective in managing potential risks of synthetic biology and maximizing its benefits. We first provide an overview of what synthetic biology is, provide some historical context, and summarize current applications of this technology in various commercial sectors. Next we provide a detailed summary of the domestic government oversight of synthetic biology. The regulation of products of synthetic biology is juggled, and not always clearly so, among three federal agencies, various federal laws, and the Coordinated Framework, which the federal government recently announced it will modernize. The regulatory framework that has evolved is complicated, increasingly circuitous, and not for the faint of heart. First-time and experienced innovators alike are increasingly vexed by the daunting jurisdictional divides crafted years ago based on fundamentally different kinds of products and technologies. We illustrate these anomalies through case studies under each of the key federal statutes -- TSCA, FIFRA, Federal Food, Drug, and Cosmetic Act (FFDCA), and PPA -- and the application of the regulatory system under each to new products of synthetic biology. These case studies crystalize the challenges regulators and innovators face in bringing new products of synthetic biology to market and the anomalous and often counterintuitive if not bewildering governance results that arise under current regulatory frameworks.

Our hope in writing this report is to support the development of synthetic biology, identify lapses in the current domestic governance of synthetic biology, and suggest solutions to ensure responsible stewardship of this technology.

COMMERCIAL APPLICATIONS OF SYNTHETIC BIOLOGY

As with many emerging technologies, applications of synthetic biology are diverse. It is clear synthetic biology is capable of delivering on its promise of clean energy, personalized medicine, pollution remediation, and other benefits. What is less clear is how the potential for harm through the inadvertent release of organisms or other bioactive materials into the environment will be prevented. To appreciate the breadth of synthetic biology's utility and better understand the reasons for both cautious enthusiasm and guarded concern, we describe below a few of this technology's diverse applications.

Agricultural and Environmental

The utility of rDNA technology is not new to the agricultural community, and plant engineering and animal breeding have been part of the agricultural landscape for years. Synthetic biology builds upon these techniques and takes them to a whole new level. Synthetic biology offers the promise of diminished reliance on chemicals that may leave damaging environmental footprints, greener grass that requires infrequent mowing, and the development of a broad array of products that enhance the efficiency of conversion, ultimately from sunlight into proteins and carbohydrates, and agricultural waste material into useful substances.

A few examples of commercial applications illustrate the diversity of synthetic biology in the agricultural sector. Monsanto Company's (Monsanto) acquisition of Agradis, Inc. in 2013, a privately-held company focusing on agricultural biologicals, reflects Monsanto's enduring interest in synthetic genomics and the utility of plant microbes to make crops more drought and disease resistant. AgraCast, another privately-held company harnessing the potential of synthetic biology, focuses on plant breeding techniques to improve the "harvestability" of castor oil and sweet sorghum crops. The Company has a business unit that is developing natural, anti-fungal products that can be used to treat fruit and vegetables post-harvest to make them mold resistant. Many of these new technologies build upon traditional rDNA technology, cloning, and related genetic engineering techniques.

Synthetic biology has many applications in the environmental arena. Engineered organisms are being developed to consume toxic chemicals in water and soil that would not otherwise decompose. Biosurfactants, naturally produced by bacteria or fungi and generally environmentally friendly to aquatic organisms, can be used to maximize the efficiency of bioremediation efforts.[1] Synthetic biofilms are being developed for use as environmental biosensors to monitor soil from environmental degradation or nutrient levels in the soil.

Healthcare

As in agribusiness, genetic engineering is no stranger to healthcare and has been used for decades in the medical community to engineer bacteria to produce insulin and accelerate the development of other vaccines. Synthetic biology is expected to enhance greatly these practices and speed and streamline new product development. With industrial fermentation processes, synthetic biology could use engineered/created microorganisms as factories to produce high qualities of medical chemicals at low cost, such as artemisinin, a malaria medication. In this case, a cluster of modified

genes taken from the mevalonate pathway of plant *Artemisia annua* are implanted into yeast that produces a precursor to artemisinin, artemisinic acid.[2]

Synthetic biology is expected to take "concierge medicine" to a whole new level. Personalized medicine seeks to harvest the potential of genomics to engineer highly specific, patient-tailored approaches to medical care. Synthetic biology will greatly enhance these efforts and promises one day to offer patient-specific solutions to medical challenges. Custom proteins "may eventually enable the delivery of 'smart proteins' or programmed cells that self-assemble at disease sites."[3] While these solutions are at the early stages of development, their utility in solving some of the many challenges healthcare poses is exciting.

Industrial Chemicals

Research using synthetic biology in the manufacture of petroleum-based plastics is underway. Polylactic acid, acrylic, and isoprene using metabolically engineered microorganisms with synthetic gene clusters are in production now. Other promising applications include the chemical *Salmonella spp*., which can be engineered with synthetic genes encoding silk monomers to produce spider silk.[4] *Saccharomyces cerevisiae* yeasts are engineered by using synthetic biology methods to produce fragrances such as synthetic vanilla, biobased succinic acid, and renewable adipic acid.

Renewable Energy

The production of biofuels and other renewable energy sources offer especially high profile opportunities to diminish reliance on petroleum-based feedstocks and reduce global warming emissions. Various alternatives to more conventional production techniques using synthetic biology include the production of cellulosic ethanol from cell walls (not corn) to produce bioalcohols using synthetically manipulated biomass.[5] Biofuels can also be produced from modified algae that rely upon photosynthesis to produce bio-oils, including biodiesel, more easily than more conventional chemical processes. Synthetic biology can improve the speed and efficiency of converting biomass into advanced biofuels using less energy and yielding more by using so-called "super-fermenting" yeast and bacteria.

Biosecurity

Biosecurity generally refers to measures needed to prevent the misuse of biological agents and organisms with the intent to do harm.[6] The National Science Advisory Board of Biosecurity, an independent federal advisory committee that advises the federal government on biosecurity issues, noted that "[b]iosecurity refers to the protection, control of, and accountability for high-consequence biological agents and toxins, and critical relevant biological materials and information, to prevent unauthorized possession, loss, theft, misuse, diversion, or international release."[7] Synthetic biology enables the precise identification of biological agents of concern that could be developed synthetically or semi-synthetically. Researchers may tag or "brand" the genetic code of new organisms with the hope that this tagging process may dissuade malicious uses of the material. Other methods, which include embedding "suicide" genes into the genome of a new organism to inhibit survival outside of a contained environment, offer a potentially more reliable means to counter biosecurity threats. Similar tools can be developed to ensure planned organism death in targeted circumstances. As with any emerging technology, uncertainties remain regarding the efficacy of such strategies as research in these applications is at an early stage of development.

CURRENT U.S. OVERSIGHT OF SYNTHETIC BIOLOGY

Coordinated Framework for Regulation of Biotechnology

There has been no new legislation enacted to address synthetic biology or related emerging technologies. Instead, the U.S. regulatory authorities have relied upon existing statutory authorizations to address new products. An overview of the pertinent federal authorities is presented below. The adequacy of these existing authorities is explored in the case studies in the next section of this report.

The federal oversight of products of biotechnology is directed through the Coordinated Framework issued in 1986 by the Reagan Administration's White House Office of Science and Technology Policy (OSTP).[8] Concern with oversight began much earlier. In 1975, growing unease with the potential for release of genetically modified organisms into the environment inspired the gathering of some 140 scientists, lawyers, ethicists, and others in Monterey, California, for the Congress at Asilomar. The Congress led to the issuance in 1976 of the National Institutes of Health (NIH) Recombinant DNA Guidelines (NIH Guidelines),[9] which offer recommendations for best practices for producers and users of genetically modified organisms. Adherence to the NIH Guidelines is mandatory for investigations at institutions that receive NIH funds doing research involving rDNA.[10]

Recognizing that many federal agencies have jurisdiction over products of biotechnology, the Coordinated Framework sets forth an organizational blueprint for federal agencies and establishes lead responsibilities for the federal oversight of products of biotechnology. The core premise of the Coordinated Framework is that the legal authorities that existed in 1986, authorities that remain largely unchanged today, provide federal regulators sufficient authority to manage any health or environmental risk the products of biotechnology may pose.

The Coordinated Framework was intended to be a flexible governance construct capable of nimbly adjusting to new science and not shackle legal authorities rigidly to specific biotechnology products. Risks are assessed on a case-by-case, product-by-product basis and focus on a product's application and its intended use, not on the technology itself. This risk-based approach is quite different from the European Union's (EU) approach, which is based on the Precautionary Principle and is likely more restrictive when applied to emerging technologies, as risks tend to be inherently more uncertain, ill-defined, and incomplete than those of more mature technologies.[11]

Under the Coordinated Framework, three federal agencies are principally responsible for regulating products of biotechnology: USDA (and, in particular, APHIS), EPA, and FDA. APHIS is responsible for regulating field trials of genetically modified crops and plants under the PPA. EPA regulates genetically engineered microbes under TSCA and genetically engineered pesticides and pesticides incorporated into plants under FIFRA. FDA regulates a broad spectrum of products, including human and animal drugs, cosmetics, dietary supplements, food, food additives, and medical devices, among others. Exactly how each agency regulates products of biotechnology, pursuant to what legal authority, and when in the commercialization process regulatory oversight attaches varies considerably. These regulatory programs are discussed briefly below.

The White House OSTP, Office of Management and Budget (OMB), U.S. Trade Representative (USTR), and the Council on Environmental Quality (CEQ) issued a memorandum on July 2, 2015, directing EPA, FDA, and USDA to update the Coordinated Framework. A July 2, 2015, OSTP blog item entitled "Improving Transparency and Ensuring Continued Safety in Biotechnology" notes that the complexity of the array of regulations and guidance documents developed by EPA, FDA, and USDA "can make it difficult for the public to understand how the safety of biotechnology products is evaluated, and navigating the regulatory process for these products can be unduly challenging, especially for small companies." The memorandum states that the objectives "are to ensure public confidence in the regulatory system and to prevent unnecessary barriers to future innovation and competitiveness by improving the transparency, coordination, predictability, and efficiency of the regulation of biotechnology products while continuing to protect health and the environment."

The memorandum states that federal agencies regulating biotechnology products "should continually strive to improve predictability, increase efficiency, and reduce uncertainty in their regulatory processes and requirements." Improvements must:

- Maintain high standards that are based on the best available science and that deliver appropriate health and environmental protection;
- Establish transparent, coordinated, predictable, and efficient regulatory practices across agencies with overlapping jurisdiction; and
- Promote public confidence in the oversight of the products of biotechnology through clear and transparent public engagement.

The memorandum initiates a process to help advance these aims, beginning with the following one-year objectives: (1) development of an updated Coordinated Framework to clarify the roles and responsibilities of the agencies that regulate the products of biotechnology; (2) formulation of a long-term strategy to ensure that the federal regulatory system is equipped to assess efficiently the risks, if any, associated with future products of biotechnology while supporting innovation, protecting health

and the environment, promoting public confidence in the regulatory process, increasing transparency and predictability, and reducing unnecessary costs and burdens; and (3) commissioning an external, independent analysis of the future landscape of biotechnology products. According to the memorandum, the following elements will support the process to achieve these objectives:

- ***Biotechnology Working Group Under the Emerging Technologies Interagency Policy Coordination Committee***: The Biotechnology Working Group will include representatives from the Executive Office of the President, EPA, FDA, and USDA.

- ***Mission and Function of the Biotechnology Working Group***: Within one year of the date of the memorandum, the Biotechnology Working Group shall take steps detailed below and others, as appropriate, to increase the transparency, coordination, predictability, and efficiency of the regulatory system for the products of biotechnology. The Working Group will:

  (1) Update the Coordinated Framework to clarify the current roles and responsibilities of the agencies that regulate the products of biotechnology, after input from the public; and

  (2) Develop a long-term strategy to ensure that the federal regulatory system is equipped to assess efficiently the risks, if any, associated with future products of biotechnology while supporting innovation, protecting health and the environment, maintaining public confidence in the regulatory process, increasing transparency and predictability, and reducing unnecessary costs and burdens.

- ***Independent Assessment***: EPA, FDA, and USDA shall commission an external, independent analysis of the future landscape of biotechnology products that will identify (1) potential new risks and frameworks for risk assessment, and (2) areas in which the risks or lack of risks relating to the products of biotechnology are well understood. The review will help inform future policymaking. Due to the rapid pace of change in this arena, an external analysis should be completed at least every five years.

- ***Budgeting for Efficiency***: EPA, FDA, and USDA shall work with OSTP and OMB, within the annual President's budget formulation process, to develop a plan for supporting the implementation of this memo in agency fiscal year (FY) 2017 budget requests and, as appropriate, in future budget submissions.

- ***Annual Reporting***: For at least five years, starting one year after the release of the strategy described above, the Biotechnology Working Group will produce an annual report on specific steps that agencies are taking to implement that strategy and any other

steps that the agencies are taking to improve the transparency, coordination, predictability, and efficiency of the regulation of biotechnology products. This report will be made available to the public by the Executive Office of the President.

The OSTP blog item states that the administration recognizes the importance of public engagement throughout this process. As part of this process, the administration will hold three public engagement sessions over the year in different regions of the country. The first listening session will occur in Washington, D.C. in fall 2015. According to the blog, the update to the Coordinated Framework will undergo public notice and comment before it is issued in final. The blog item includes a link to sign up to be kept up to date on these activities.

Federal Food, Drug, and Cosmetic Act

The Food and Drug Administration's (FDA) oversight under the Federal Food, Drug, and Cosmetic Act (FFDCA) is vast. According to FDA, 20 cents of every dollar spent in the U.S. relates to products FDA oversees.[12] The legal and regulatory framework pertinent to any specific commercial product varies considerably and, as such, complicates an effort to draw useful general rules that will apply to the products of new technologies.[13] As discussed in depth in an insightful scholarly analysis, a consistent theme running throughout the regulatory construct is that governance under the FFDCA largely turns on the concept of a statutorily defined "product" rather than a defined manufacturing process of which the product of concern is an endpoint.[14]

As the Paradise and Fitzpatrick article discusses, the rigidity of an approach driven by statutorily defined "products" makes it less than nimble in the context of synthetic biology. Both the inflexibly defined products and the separate FDA "Centers" that regulate them contribute to a balkanization of the review process. The inevitable, compart-mentalizing "silo" effect that results from this approach poses recurring challenges to FDA's ability effectively to oversee products that straddle the definitional bright lines that were drawn by Congress decades ago, well before synthetic biology and other emerging technologies became real-world regulatory puzzles.

FDA oversight of a "product" is premised on the concept of intended uses. How a material is used dictates the process to be followed for the material's regulatory approval, if any. The approval process for a cosmetic ingredient use, for example, is considerably different from the approval process for the same substance's use as a food additive. As science and biotechnology evolve, new approaches to producing drugs, food additives, and cosmetics are rapidly emerging. Regulatory initiatives and new laws, including the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the Food Safety Modernization Act of 2011 (FSMA), expand upon the ways FDA can improve its governance to address scientific advances. The core regulatory construct under the FFDCA, however, and the enormous regulatory bureaucracy built around it challenge the efficient and comprehensive review of products of all new technologies, including synthetic biology.

A detailed overview of FDA's authority to evaluate products of biotechnology is beyond this report's scope. An excellent summary of FDA's regulation authority is found in the Venter Report.[15] As noted in that report, FDA's authority is limited to assessing human and animal health as FDA has no authority to assess the impact of products of biotechnology on broader ecosystems. FDA regulatory decisions may trigger environmental impacts addressed under the National Environmental Policy Act (NEPA), but NEPA bestows no new authority to FDA or other federal agencies to address any potential risks that may be identified.[16]

Products of synthetic biology are subject to FDA regulation in several contexts. Biotech-

nology-derived drugs and medical devices have been routinely renewed by FDA going back to the early 1980s,[17] and they will be of increasing interest now and in the foreseeable future due to the ever-growing research activities in these areas and initiatives to commercialize them. FDA makes no distinction between traditional recombinant techniques and synthetic ones. "Drug" is the fundamental, statutorily-defined term that underpins FDA's regulatory activities in this area. For purposes of the FFDCA, it means, in relevant part:

> (A) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and
>
> (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
>
> (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and
>
> (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). . . .[18]

FDA has long recognized and regulated biologics, a sub-set of drugs derived from living materials -- human, animal, or microorganisms. Chemically synthesized small molecular weight drugs generally have a well-defined structure and can be thoroughly characterized. In contrast, biological products are complex in structure, and thus are usually not fully characterized.[19] FDA generally regulates most familiar biological products -- such as insulin, glucagon, and growth hormone -- under the same regulations and rubrics as traditional small molecule drugs.

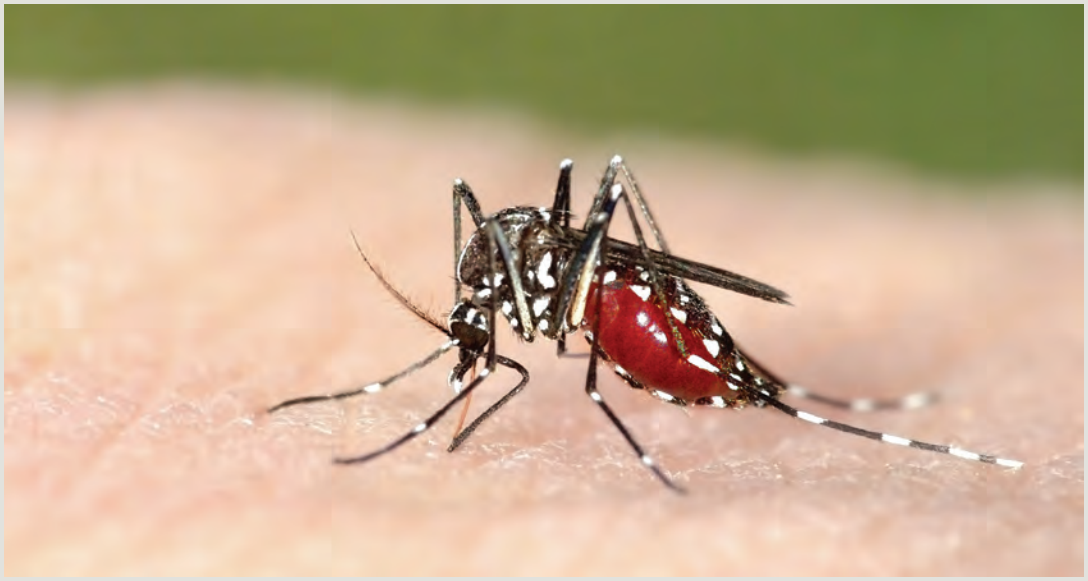
The regulatory pathway then splits, based on whether the article involved is a "new drug" or a "new animal drug," although both are subject to pre-market testing requirements to demonstrate safety and efficacy before they can be commercialized, and previously-approved applications may be withdrawn for a variety of reasons after notice and an opportunity for comment. Post-approval oversight of manufacturers' obligations in the case of human drugs has been a matter of increasing focus.[20]

An application for a new human drug (NDA) will be subject to FDA's most thorough and rigorous pre-approval testing, which requires a commitment of time and substantial expense for the developer. A new animal drug application (NADA) will follow a pathway that is similar in many, but not all, respects, including a less extensive post-market oversight regime. To the extent that animals -- and animal "drugs" -- come to reflect the products of genetic engineering, it is highly likely FDA will pay more attention to activities in this realm. The Paradise and Fitzpatrick article cites FDA's articulated position that once an NDA or an NADA for an rDNA drug obtains approval, a food that bears or contains that rDNA drug "is not considered adulterated if used in accordance with the conditions and indications approved by the FDA."[21] This includes "an rDNA construct" in a genetically engineered animal, including animals used for food, for which FDA approval has been granted. "Thus," according to Paradise and Fitzpatrick, "the

FDA will approve two articles when the product is a food that humans will consume: (1) the construct as an animal drug and (2) the food containing that construct as a food safe for human consumption."[22] FDA then, as required, will amend its animal drug regulations accordingly. Paradise and Fitzpatrick point to regulations adopted for rDNA products in goat's milk as an example of what must occur from a regulatory standpoint and observes that, to date, the rDNA goat's milk regulation is the only entry in FDA's regulations on new animal drugs in genetically engineered animals.[23]

Where FDA is asked to oversee a different category, or categories, of products in a regulatory framework that pre-dates them, the role of agency guidance can be vital to developers seeking to devote resources appropriately and also to ensuring that safety concerns throughout the lifespan of the product are explored and addressed. In a series of guidance documents issued in June 2014, FDA has taken initial steps to address new and/or novel technologies and existing substances in its oversight role.[24] While these FDA guidance documents focus specifically on nanotechnology, the message is equally applicable to other emerging fields, including synthetic biology. A specific *Guidance* document alerts manufacturers to the potential impact of any significant manufacturing process change on the safety and regulatory status of food substances. FFDCA requires industry to consider the basic fundamentals under Sections 402 and 301 (adulteration and misbranding, respectively) and this *Guidance* reminds the regulated community that "it is the responsibility of both the manufacturer and the end user of a food substance to ensure that the use of the food substance is safe and lawful."[25] Identity, technical effect, self-limiting levels of use, dietary exposure, and manufacturing processes are a few of the considerations explored by FDA in this *Guidance*, which should be required reading for developers of new technologies subject to the FFDCA.

Applications of synthetic biology used to produce food additives or cosmetic ingredients[26] invite many questions about these factors in the evaluation process much like the inclusion of nanomaterials on a manufacturing process. Cosmetics in most instances are not heavily regulated by FDA, but the presence of "something new" may bring an otherwise ordinary cosmetic into FDA's regulatory ambit. Whether producing a flavor additive or a cosmetic ingredient, for example, using synthetic biology results in something new that requires pre-market approval by FDA is unclear in the abstract, but it poses an issue of which to be aware. An additive that is intended to alter certain food properties is considered to have a "technical effect" and thus requires pre-market review prior to use. Changes in a food additive could result in alterations to the food that could materially impact assumptions made during the pre-market review process and upon which the approval, in part or whole, was based. It is not always clear, however, who exactly decides, and what changes trigger a technical effect that would occasion FDA's regulatory oversight. It is precisely for this reason FDA issued the *Guidance,* which is just that, guidance and not binding on the agency.



Oxitec Case Study

Context

The yellow fever mosquito, known as *Aedes aegypti (A. aegypti)*, has been known to carry and transmit viruses, including yellow fever, dengue fever, and chikungunya, according to the Centers for Disease Control and Prevention (CDC).[27] *A. aegypti* is native to Africa, but has spread to other tropical and subtropical regions, where it prefers to occupy and produce offspring in open waters with organic matter near populated residential areas. Only the female mosquitos bite and must feed on blood, preferably (but not limited to) human blood, to lay eggs. This feeding behavior of the female mosquito is a key element in the transmission of disease to humans. The lifespan of the *A. aegypti* is around three weeks. Its eggs, however, can survive in favorable climates for six months or longer.

Current methods for controlling populations of these mosquitos include eliminating their preferred habitats (standing water in and around homes); wearing protective clothing to prevent bites (*i.e.,* long sleeve shirts, pants, socks); applying insect repellents; and spraying pesticides. Spray application of pesticides is documented as achieving approximately 50 percent reduction in mosquito populations.[28] This low reduction rate is attributed to their preferred habitat being in close proximity to residential homes and the difficulty in eradicating them using spray methods.

Description of the new technology

Oxitec, Ltd. (Oxitec), a privately-held company organized under English law,[29] has developed a genetically engineered mosquito strain by micro-injection of rDNA into *A. aegypti* eggs designed to kill the subsequent offspring.[30]

The Oxitec rDNA construct contains a dominant lethal gene that is repressed in the presence of adequate concentrations of tetracycline. Mosquitos expressing the rDNA transgene are dependent upon the presence of tetracycline for their survival. Viable adults resulting from the micro-injected eggs were mated in the laboratory to wild-type mosquitos, and the resulting hatched larvae were screened for expression of the fluorescent marker that was also coded in the rDNA plasmid vector. The heterozygous transgenic strain is described as having a single copy of the rDNA construct at a single site in the mosquito genome. Transgenic heterozygotes are sorted by sex at the pupal stage and, for purposes of implementing the insect control approach dubbed Release of Insects carrying a Dominant Lethal (RIDL),[31] males would be released from the controlled environment of the insectary (lab) into the wild to mate with wild *A. aegypti* females before dying due to the de-repression of their dominant lethal gene in the absence of sufficient dietary tetracycline that is available in their supplemented feed within the insectary, but not in the wild. Half of the progeny of these RIDL/wild type crosses are expected to be RIDL heterozygotes, and half are expected to be wild type. In the absence of dietary tetracycline supplementation, however, the RIDL larval offspring will die before reaching the pupal stage, whereas the wild type offspring will be unaffected genetically, but may suffer adverse effects due to competition for nutrients with the doomed RIDL larvae. According to Oxitec, releasing the appropriate number of RIDL males into the wild could achieve an overall 90 percent reduction in the treated *A. aegypti* population.

Sterilization for population reduction has had favorable results in controlling insect populations in other species, but has not been possible for mosquitos due to technical and regulatory issues. The genetic modification of these RIDL mosquitos includes a fluorescent marker for tracking them once they are released into the wild, as well as the tetracycline controlled kill mechanism used to limit the lifespan of the modified transgenic mosquitos and, in the absence of genetic recombination events, preventing the transmission of the rDNA construct to future generations of *A. aegypti* in the wild. The low transformation efficiency described for this rDNA construct in Phuc's 2007 publication suggests that spontaneous genetic recombination between the rDNA construct and wild type DNA is unlikely, but this is one of the points that must be addressed with actual data during the regulatory approval process. Phuc's 2007 publication's description of the strain from which the current Oxitec transgenic mosquitos are derived also notes that 3-4 percent of the progeny resulting from breeding transgenic males with wild type females resulted in transgenic adults that survived in the absence of tetracycline. The precise genetic status and reproductive capabilities of transgenic mosquitos that do not express the dominant lethal trait in the absence of tetracycline is also important in the assessment of this novel technology.

Discussion of the legal and procedural issues

FDA defines "drug" to mean an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" and/or

an article "intended to affect the structure or any function of the body of man or other animals."[32] The introduction of a new modification to the structure or function of the body of man or animal is, by FDA definitions, creation of a new drug. The management of drugs within FDA is divided between new human drugs, as administered by the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER), and new animal drugs, as administered by the Center for Veterinary Medicine (CVM). New animal drugs are drugs intended for use in animals other than man; animals are further divided into minor and major species. FDA includes cattle, horses, swine, chickens, turkeys, dogs, and cats among major species and designates all other animals as minor species. FDA defines genetically engineered animals as "those animals modified by rDNA techniques, including the entire lineage of animals that contain the modification."[33] The Oxitec genetically engineered *A. aegypti* strain could be regulated by FDA as both a minor species new animal drug that is subject to pre-market notification processes through CVM and as an article for the mitigation of disease in man that is subject to the requirements for new human drugs.

CVM guidance for genetically engineered animals (GFI 187) indicates that all genetically engineered animals are subject to pre-market approval requirements. FDA has indicated that, in certain cases, it may not enforce the requirements for an investigational new animal drug (INAD) or a NADA and intends, in such cases, to post this on its website. FDA is always authorized to initiate enforcement action if the agency becomes aware of a safety concern. In 2003, FDA posted a statement for aquarium fish that were modified to contain genes that were fluorescent and not for food use. FDA concluded that this use of a genetically engineered animal posed no more of a threat than their "unmodified counterparts."[34] FDA conducts a review to comply with NEPA when it reviews and approves an INAD or NADA. NEPA requires federal agencies to describe in detail and assess the anticipated impacts of all "major Federal actions significantly affecting the quality of the human environment."[35] No NEPA review would occur, however, when FDA exercises its enforcement discretion.

The Oxitec example in this case study is unique in many ways. The field trials Oxitec proposed include the release of a genetically engineered minor species into the environment for population control of insects carrying human diseases. Release of genetically modified insects to mitigate human disease is relatively uncharted territory for FDA. The release into the wild means FDA's enforcement discretion will not be exercised, and that CVM will enforce full pre-market approval as a new animal drug. The decision regarding CVM jurisdiction with this case study has been, and continues to be, debated. Genetically engineered insects being developed for plant pest control are considered under the oversight of USDA's APHIS. Previously approved FDA anti-malaria drugs manufactured using synthetic biology techniques were managed by CDER/CBER, not CVM. The reason for this decision is that the drug for mitigation of human disease was

produced by a modified organism, rather than the modified organism mitigating the species responsible for causing the disease. The Oxitec mosquito could be considered an article for mitigating disease. Environmental group Friends of the Earth (FOE) opines in an Issue Brief on this matter that this intended use of genetically engineered mosquitos "should be considered a medical trial and must follow the strict laws and guidelines in place to protect human subjects in medical trials."[36] FOE believes that this includes free and informed consent by all humans in the release area.[37]

GFI 187 indicates a new animal drug is deemed unsafe unless FDA has approved it through a NADA for that particular use. There are exemption processes for conditional approval and indexing unapproved investigational animal drugs for the purpose of pursuing safety and effectiveness investigations by trained scientific experts. The Minor Use and Minor Species Animal Health Act of 2004 also provides additional options for streamlined pre-market approval for minor species and treatment of uncommon diseases in major animals. None of these exemptions or streamlined approaches applies to genetically modified animals.[38] The NADA process involves a detailed demonstration that the drug in its intended use is safe and effective, not only to the animal itself, but also to any food products derived from the treated animal. The process also includes consideration of potential environmental impacts and safety assessments for those responsible for administration of the drug.

Developing a NADA requires extensive technical data supporting the proposed dosage, intended use, and potential environmental impact information. The process is typically done in cooperation with CVM's Office of New Animal Drug Evaluation through the opening of an INAD file. There is a fee structure associated with these activities as required through the Animal Drug User Fee Act of 2003 (ADUFA).[39] This fee structure also includes detailed timelines for responses the agency must provide for the various aspects and steps of the NADA process.

The NADA general application provisions are detailed in 21 C.F.R. Part 514. The requirements generally include the following:

Basic identification details on the nature of the application, and the trade name and location of the applicant. For genetically engineered animals, the details on the rDNA construct, including the number and characterization of the insertion sites is also necessary.

A summary of the chemistry, clinical purposes, and laboratory and clinical studies is included.

Proposed labeling for adequate instructions for use must accompany the application. The labeling for genetically engineered animals should include a description of the common name, genus, and species with instructions for handling throughout the animal's lifecycle.

Details on the composition and components utilized in the production of the drug. The GFI 187 recommends providing the molecular characterization of the article in sufficient detail to facilitate evaluation of potential risks due to genetically engineered animal rDNA that might encode pathogens, toxicants, allergens, mobile DNA sequences, or sequences that deregulate growth control.

Extensive details on the manufacturing methods, production facilities, and controls to allow for sufficient evaluation that the methods described will "preserve the identity, strength, quality and purity of the new animal drug" are to be provided.[40] Evaluation of any "interruption of a coding or regulatory region (insertional mutagenesis)" is also recommended in the GFI 187.[41]

CVM could, upon request, also require four identical sets of representative samples for each strength of the finished dosage with all the articles used as components along with reference standards and detailed analytical assaying procedures used to determine quality specifications. This can include detailed experimental protocols for establishing dosage, and when used in animals that are also a food source, substantial information on tissue residuals and elimination rates. Samples of the genetically engineered animal could also be required, upon request. CVM encourages specific dialogue as part of the INAD file, as to how to address this aspect of the application process.

The application is to include evidence of the establishment of safety and effectiveness, including proposed labeling. This evidence must include reports of all the tests, scientific literature, and clinical investigations utilized to support the claims, including favorable and unfavorable results.

Commitments to manufacture in accordance with current Good Manufacturing Practices (cGMP) and conform to advertising requirements are included in the application. FDA has indicated it will provide guidance for how genetically engineered animals are to "commit to cGMP" aspects of this process at a later date. Non-clinical studies are expected to be conducted in compliance with the Good Laboratory Practice regulations in 21 C.F.R. Part 58, and the reason for any non-compliance must be provided.

Each application is to include a claim for categorical exclusion or an environmental assessment that demonstrates that the new animal drug or the genetically engineered animal will not significantly impact the quality of the human environment.

These details are assembled in accordance with 21 C.F.R. § 514.1(b)(15), and submitted to CVM for review.

Conferences with CVM prior to submission of a NADA are described in 21 C.F.R. § 514.5 and include conducting field studies, if necessary. Oxitec is currently seeking approval to conduct field studies within the United States. Oxitec reports field trials have been and are ongoing in other locations, and discussions are currently ongoing with FDA as part of their INAD. The NADA approvals in general are carried out in stages, and the reviews involve experts in many areas of science, including veterinarians, animal scientists, biostatisticians, chemists, microbiologists, pharmacologists, and toxicologists.[42] All aspects are reviewed, including the product's final labeling, packaging, and possible directions for use, prior to CVM approval. Review of genetically engineered animals may involve inclusion of addition technical experts and possible interaction with other agencies (*i.e.*, EPA, CDC, and USDA). Interactions with EPA and CDC have

been part of the ongoing Oxitec field trial discussions within CVM. After the NADA is complete, the approval process requires notification through the *Federal Register*. Once approved and listed in the *Federal Register*, any significant changes as detailed in 21 C.F.R. § 514.8 must be re-substantiated through a supplemental approval process.

All approved animal drugs are expected to maintain all aspects of the processes detailed in their application in accordance with FDA regulations at all times, and are subject to inspection. All adverse events are to be investigated and reported. Drug listing, recordkeeping, and periodic reporting are all required post-approval. Any significant deviation in quality controls, equipment, facilities, labeling, etc., must be reviewed and approved prior to sale or distribution.

The legal and regulatory takeaway

The intricate details and ongoing jurisdictional debate are interesting parts of this complex case study. An argument could be made that a technology designed to control a pest should be regulated by FIFRA. As discussed, past genetically engineered pest control technologies have fallen under the jurisdiction of APHIS. Technologies that control animal populations by sterilization, however, have been regulated by CVM. Some argue that if the Oxitec mosquitos are primarily intended to prevent or mitigate a human disease, the product should be regulated as a human drug rather than as an animal drug.

After review and consultation, however, the various regulatory authorities determined that the Oxitec mosquitos are most appropriately regulated by CVM as an animal drug. CVM's precedent of regulating other animal sterilants used for animal population control as animal drugs is guiding FDA and the other regulatory stakeholders in determining a regulatory pathway for the Oxitec mosquito. As with almost all FDA-related regulatory inquiries, of equal importance is the initial determination of the product's "intended use." Here, Oxitec and other stakeholders have been careful to describe the use of the product as limiting or controlling the population of certain mosquitos. Notably, the product makes no claim to prevent or mitigate disease in humans; the product only claims to control or reduce the population of certain mosquitos.

The Oxitec mosquito control technology is a novel case for CVM because it employs rDNA technology in an organism that is intended to be released into the wild, not simply used to produce an animal drug that would then be used under controlled conditions. Nonetheless, limiting the Oxitec product's claim to one already within the ambit of CVM's prior regulatory experience supports the rationale for regulating the Oxitec mosquito as an animal drug. Any future claims that this technology prevents or mitigates human disease -- such as dengue fever or chikungunya -- rather than simply controlling a mosquito population would likely raise questions of whether the technology is a human drug, and thus subject to CDER jurisdiction.

Given the complexity of the jurisdictional gauntlet, it is completely unclear how a new product developer would begin the regulatory approval process, as none of these issues is intuitively self-evident. Little guidance exists to direct private entities to the appropriate government office to begin the review process, let alone outline what that

process is, how long it might take, and how much it might cost before the product can be commercialized. These are business realities that must be known to bring a product to market. This case study crystalizes just how unclear the jurisdictional divide is and how even the government can be at a loss to specify which agency has the lead, let alone outline coherently what the review process might include.

Synthetic Squalane Case Study

Context

Squalane -- a cosmetic ingredient that functions as an emollient in lotions and moisturizers -- has been used as a softener for more than 25 years, according to the Personal Care Council's Cosmetic Ingredient Review (CIR).[43] Squalane is the saturated branched chain hydrocarbon form of squalene. The CIR indicates squalene is a triterpene polyunsaturated aliphatic hydrocarbon that is naturally occurring in large quantities in shark liver oil and other fish oils and in smaller amounts in plants (*i.e.*, olive oil, wheat germ oil, rice bran oil, palm oil). Squalene also exists in humans as a component of sebum, an oily fluid produced by the sebaceous glands.

As shark liver oil contains the greatest yield potential for squalene, the manufacturing process to produce squalane often involves molecular distillation of shark liver oil and hydrogenation of the distillate, followed by a re-distillation step to produce a purity of about 96 percent squalane. The use of shark liver oil is controversial as some species of shark are listed as endangered and/or threatened by the U.S. Fish and Wildlife Service.[44] Manufacturing squalane using plant sources is an alternative option. Indications are the squalene concentrations are much

lower in plant sources and costs can be prohibitive for cosmetic formulators.

Description of the new technology

As reported in the New York Times on May 30, 2014, a synthetic biology version of squalane, manufactured by biotechnology firm Amyris, is commercially available for use as a cosmetic ingredient.[45] Amyris, according to its website, uses "synthetic biology to produce target molecules."[46] Based on public information, the production appears to involve proprietary yeast strains that convert sugar to produce various hydrocarbons of interest, in this case, squalane.

Discussion of the legal and procedural issues

FDA regulates cosmetics and other substances under the FFDCA. Under FFDCA, cosmetics are defined to include "(1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles."[47] Soap, as defined by FFDCA, is excluded from the definition of a cosmetic because of compositional distinctions and intended uses and is regulated separately by the Consumer Product Safety Commission.[48] FDA regulates cosmetics in commerce under its FFDCA authority in conjunction with the Fair Packaging and Labeling Act (FPLA) as administered by the Federal Trade Commission (FTC). Cosmetic ingredients and finished cosmetics, with the exception of color additives, do not require FDA approval prior to use in commerce. There are specific ingredients that are prohibited for use in cosmetics[49] and FDA considers any ingredient that can impart a therapeutic response or affect the structure or function of the body to be a drug, not a cosmetic.

For squalane, the intended use as an emollient in lotions and moisturizers would be considered within FDA's jurisdiction as a cosmetic ingredient, provided the intended use does not violate the fundamental concepts described above (e.g., does not imply a therapeutic or drug use), and it otherwise comports with the basic principles of adulteration and misbranding as defined in FFDCA Sections 402 and 301. Cosmetic manufacturers are expected, but not required, to comply with the FDA general principles of Good Manufacturing Practices (GMP). FDA has developed a draft guidance document[50] for the GMP process that provides non-binding recommendations for companies intending to manufacture cosmetics in compliance with GMPs. Under the general misbranding and adulteration provisions of the FFDCA, however, FDA has the authority to pursue enforcement actions against cosmetic products that are not compliant with the law or regulations. The burden of safety and demonstration of intended use fall squarely on the cosmetic industry.

Finished cosmetics are required to be labeled correctly in accordance with FDA and FPLA statutes and regulations. Cosmetic claims on the product label, in promotional literature, advertising, trade press, and packaging are critical in assessing compliance with technical

regulatory provisions and in determining a product's intended use. The requirements are set forth in 21 C.F.R. Parts 701 and 740. The requirements for the declaration of ingredients are found in 21 C.F.R. § 701.3. FDA states that the ingredients must be identified in one of the following ways: by being specifically mentioned in 21 C.F.R. § 701.30; as defined by the Cosmetic, Toiletry and Fragrance Association, Inc. (CTFA), the United States Pharmacopeia (USP), National Formulary, Food Chemicals Codex, U.S. Adopted Names (USAN), and USP dictionary of drug names; or in absence of being specifically listed, through the use of a name that is generally recognized by consumers or a chemical or other technical name.[51] In this case, the labeling declaration requirements on the finished cosmetic could raise an issue of proper identification with respect to the synthetic biology squalane because there is no recognized or accepted standard to identify and distinguish squalane produced through synthetic biology.

The legal and regulatory takeaway

A key issue is whether squalane produced using synthetic biology and generated from engineered yeast rather than derived from known historical sources (such as shark or olive oil) is considered the same ingredient for regulatory purposes as those currently in commercial use in marketed cosmetic products. Or, conversely, is the synthetic biology version something different and more appropriately described using a descriptive generic name? The compliance issue for the cosmetic industry and FDA could be one of interpretation of FDA's current labeling and enforcement requirements: Is an ingredient derived from synthetic biology but labeled in the same manner as a substance usually extracted from conventional sources misbranded as defined in Section 301?

An even more consequential issue for the private sector is that FDA's authority in the area of cosmetics and cosmetic ingredients is more limited than in other areas, such as for drugs or biologics. FDA currently lacks authority to require pre-market approval for cosmetic ingredients (except for color additives). Moreover, FDA's approach for oversight tends to be reactive rather than proactive for this category of product. In short, cosmetics -- whether produced conventionally or through synthetic biology techniques -- are not subject to regulatory risk assessment prior to market entry, yet the products are distributed and used by consumers, arguably the most vulnerable and least aware of the consequences of exposure and misuse. The regulatory burden remains solely with the cosmetic industry to demonstrate cosmetic and cosmetic ingredients are safe and do not impart any poisonous or deleterious substances that could result in injury to the health of the user, or consist, in whole or in part, of filthy, putrid, or decomposed substances.

FDA regulates cosmetic ingredients, whether conventional or from synthetic biology, primarily through a process that allows FDA to take action after a product is on the market if there is evidence that it is causing harm to humans or animals. Guidance for industry on FDA's "current thinking" about how cosmetics can be manufactured in accordance with GMPs is available, but compliance is not mandatory.

The key regulatory tools available to FDA to regulate risk from cosmetic products are enforcing ingredient labeling and product claims. Currently, products that include ingredients like squalane derived from synthetic biology use conventional labeling and nomenclature to identify them. FDA has not yet addressed whether cosmetic ingredients from synthetic biology are sufficiently the same as those from conventional sources to allow use of the same nomenclature.

The claims used to describe the attributes of ingredients produced from synthetic biology may also present a novel enforcement issue for FDA and industry. It is unclear, for example, whether it is appropriate and non-misleading under FDA and the FTC's regulations to claim an ingredient is "natural" if it is the product of genetic manipulation of a non-conventional source. Similarly, it is unclear whether identification of the squalane source included in the ingredient label renders the product misbranded for failure to comply with FDA cosmetic labeling regulations.

As the cosmetic industry expands its use of synthetic biology in formulating ingredients and products, it is essential carefully to monitor enforcement trends and policy statements from both FDA and FTC. As these agencies grapple with the implications of synthetic biology in the context of their current, limited and somewhat outdated regulatory structures, it would be prudent for industry to exercise judicious scrutiny of ingredient labeling and proposed claims for cosmetic products to avoid any potential interpretation that would describe a therapeutic intention (potentially rendering the product an unapproved new drug) or fall beyond the scope of required labeling (potentially misbranding the entire product).

Federal Insecticide, Fungicide, and Rodenticide Act

Pesticides are regulated by the Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)[52] and the FFDCA,[53] as amended in 1996 by the Food Quality Protection Act (FQPA).[54] FIFRA defines a pesticide broadly as "any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest."[55] EPA regulations further define the term "pesticide" as "any substance (or mixture of substances) intended for a pesticidal purpose, *i.e.*, use for the purpose of preventing, destroying, repelling, or mitigating any pest."[56] FIFRA defines the term "pest" broadly to mean "(1) any insect, rodent, nematode, fungus, weed, or (2) any other form of terrestrial or aquatic plant or animal life or virus, bacteria, or other micro-organism (except viruses, bacteria, or other micro-organisms on or in living man or other animals)."[57] In addition to a chemical substance, as that term is commonly understood, a pesticide substance also may be a microbial agent[58] or a plant-incorporated protectant (PIP).[59]

FIFRA is heavily reliant upon the concept of intended use. EPA considers a substance to be intended for a pesticidal purpose, and thus to be a pesticide requiring registration, if: (1) the person who distributes or sells the substance claims, explicitly or implicitly, that the substance can or should be used as a pesticide or consists of or contains an active ingredient and can be used to manufacture a pesticide; (2) the substance consists of or contains more active ingredients and has no significant commercially valuable use as distributed or sold other than use for a pesticidal purpose, by itself or in combination with any other substance, or use for manufacture of a pesticide; or (3) the person who distributes or sells the substance has actual or constructive knowledge that the substance will be used, or is intended to be used, for a pesticidal purpose.[60]

Under FIFRA, new pesticides must be registered with EPA before they can be commercially marketed. As FIFRA is a risk/benefit statute, EPA must balance the benefits offered by a pesticide against any potential risks it might pose in making the registration decision. It is noteworthy, however, that registration of a pesticide for food uses where there are pesticide residues requires the establishment of a tolerance, and the standard applicable to that tolerance decision does not require a benefits assessment.

More specifically, to register a pesticide under FIFRA, EPA must determine, among other issues, that the pesticide when used as intended "will not generally cause unreasonable adverse effects on the environment" when the pesticide product is used as intended. FIFRA defines the term "unreasonable adverse effects on the environment" to mean: "(1) any unreasonable risk to man or the environment, taking into account the economic, social, and

environmental costs and benefits of the use of any pesticide, or (2) a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under section [408 of the Federal Food, Drug, and Cosmetic Act.]"[61] In other words, benefits are to be taken into account for the FIFRA decision itself, but if a food use tolerance is required for a particular registration, however, EPA must also find with "reasonable certainty" that "no harm will result from aggregate exposure to the pesticide residue."

Persons wishing to register a pesticide under FIFRA must provide significant data demonstrating that the product meets the applicable EPA safety and registration standards, much of it specifically enumerated in EPA regulations and guidance documents. Because FIFRA is product and application specific, EPA has significant authority over products considered to be pesticides, even when emerging technologies are involved. The American Bar Association (ABA) analyzed FIFRA's authority to oversee pesticidal products using nanotechnology, another emerging technology, and determined that EPA has considerable authority under FIFRA to prohibit, condition, or allow the manufacture and use of nanopesticides. Its regulatory tools include regulation of pre-registration research and development (R&D) through EUP; requirements for pre-registration testing; the registration requirement, which requires development of data and can impose limits on the use and handling of a nanopesticide; requirements for registrants to submit post-registration adverse effects information; possible requirements for post-registration testing; and reregistration requirements. Additionally, EPA has strong enforcement options under FIFRA to proceed against unregistered nanopesticides or those found to cause unreasonable adverse effects on human health or the environment. EPA therefore has the authority under FIFRA to prohibit the use of nanopesticides presenting unreasonable adverse effects, and may restrict other nanopesticides so as to ensure that risks do not become unreasonable.

EPA's Office of Pesticide Programs (OPP) is organized into various divisions. The Biopesticides and Pollution Prevention Division (BPPD) reviews applications for the FIFRA registration of pesticides derived from natural materials and microorganisms. In general, there are three categories of biopesticides. Microbial pesticides are pesticides that have a microorganism as the active ingredient. *Bacillus thuringiensis* (Bt) is an example. The bacterium produces a protein that in turn kills the larvae of targeted insects. Biochemical pesticides are naturally-occurring substances that control pests by nontoxic mechanisms; they include hormones, natural plant regulators, and pheromones. These nontoxic mechanisms interfere with the growth or mating of targeted pests. A PIP is a pesticidal substance that plants produce from genetic material that has been added to the plant. EPA provides as an example taking the gene for the Bt pesticidal protein and introducing that gene into a plant's own genetic material. With the introduction of the gene, the plant, instead of the Bt bacterium, manufactures the substance that controls targeted pests. EPA states that in this instance, the protein and its genetic material, but not the plant itself, are regulated by EPA. These genetic materials can be introduced to plants either through conventional breeding techniques or through

more modern biotechnology techniques.

Under FIFRA, the statutory definition of pesticide turns on the intent of the manufacturer to produce a pesticide, not on its manufacturing process. Accordingly, EPA has interpreted its regulatory authority to include plants that have been genetically modified through rDNA techniques as they are substances that are fundamentally intended for "preventing, destroying, repelling, or mitigating any pest" within the statutory definition of the term under FIFRA. EPA has articulated its position in a series of *Federal Register* notices that describe its legal position.

EPA's regulatory program for the registration under FIFRA of biopesticides and natural and genetically modified microbial materials is comprehensive and well-defined. Research activities are also regulated by EPA, but less robustly. Under the controlling rules, with exceptions for certain types of testing that meets specified criteria for research testing, notification must be submitted to EPA at least 90 days before conducting a small scale test of a genetically modified microbial pesticide other than those otherwise exempted. Containment and monitoring methods must be specified in the notice.[62] The Biotechnology Notification Process (BNP) for release of a genetically engineered microbial pest control aspect requires review and approval by EPA prior to commencing experimentation.[63] The review process is relatively short as EPA intended the BNP to apply to smaller field test plots of less than an acre.

Registration under FIFRA Section 3 for a microbial pesticide is data intensive. The requirements are set forth at 40 C.F.R. § 158.2120-.2150 and consider, among other endpoints, potential adverse effects to non-target organisms, environmental fate of the microorganism, toxicity, and pathogenicity. EPA issued the first Section 3 registration for a microbial pesticide under FIFRA to Mycogen Corporation in 1991 for two pseudomonas fluorescent strains that were genetically engineered to express two types of delta endotoxin genes from Bt for insect control. The registration process for this product began at least five years earlier when Mycogen began working with EPA on

Biopesticide Case Study

small scale field testing.

Context

Pesticides regulated under FIFRA by EPA include what may be considered "conventional" pesticides and pesticides derived from natural materials and microorganisms. Biopesticides are divided into three groups -- microbial pesticides, biochemical pesticides, and plant-incorporated protectants -- and are typically considered by EPA to be "reduced risk pesticides" because of their non-toxic mode of action. While EPA may have developed programs to encourage the registration of biopesticides, there are ongoing challenges in determining jurisdiction, assessing the safety of experimental trials, and ultimately determining that the biopesticide will not cause unreasonable adverse effects to human health or the environment.

Description of the technology

Pheromones are chemicals secreted by both humans and animals that trigger a social response from members of the same species (attracting potential mates or in ants being able to lead others to a food source). While they have long been used as effective attractants for traps, pheromones are often difficult and expensive to synthesize. In 2014, an International Genetically Engineered Machine Foundation (iGEM)[64] team from the National Chiao Tung University[65] in Taiwan realized that if they could stimulate female insects to overproduce pheromones, the females themselves could be the bait that lures males into a trap. In nature, female insects produce Pheromone Biosynthesis Activating Neuropeptide (PBAN) to stimulate

the synthesis of pheromones[66] to attract males for mating. The iGEM team, which was a finalist for the grand prize in the international undergraduate student synthetic biology competition, developed a genetically modified strain of *E. coli* that produces PBAN. The team mixes the synthetically derived PBAN with a sugar solution, which is then placed in a trap as food. Female moths enter the trap and eat the sugar solution containing PBAN. The PBAN ingested by the female moths induces them to produce pheromones, which then attracts male moths into the trap. As long as the females ingest the sugar/PBAN mixture, they will continue to produce pheromones and attract males.

Discussion of the legal and procedural issues

Biochemical pesticides are among the biopesticides regulated by EPA. These pesticides are naturally-occurring substances that control pests by non-toxic mechanisms and include hormones, natural plant regulators, and pheromones. Substances or articles intended to control bacteria and fungi in or on living humans or animals are not intended for use against "pests" and thus are not pesticides regulated under FIFRA. Instead, such substances are regulated under FFDCA by FDA.

Under the controlling rules, EPA would take the position that the use of a biopesticide in a trap for purposes of mitigating (*i.e.,* interfering with the growth or mating of targeted pests) a pest (*i.e.,* moth) would require registration under FIFRA. On the other hand, EPA has determined that certain pesticides are not of a character requiring FIFRA regulation. Among those substances are "[p]heromones and identical or substantially similar compounds labeled for use only in pheromone traps (or labeled for use in a manner which the Administrator determines poses no greater risk of adverse effects on the environment than use in pheromone traps), and pheromone traps in which those compounds are the sole active ingredient(s)."[67] Synthetically produced compounds are considered "identical" to a pheromone when "their molecular structures are identical, or when the only differences between the molecular structures are between the stereochemical isomer ratios of the two compounds, except that a synthetic compound found to have toxicological properties significantly different from a pheromone is not identical."[68] There is an important, but subtle, distinction in this case: FIFRA exempts pheromones, but PBAN is not a pheromone. PBAN is a hormone that acts upon female moths to stimulate pheromone production, so PBAN itself is not eligible for the pheromone exemption and is regulated by FIFRA.

If use of PBAN were not regulated under FIFRA (*i.e.*, if it were a pheromone), it could be subject to the provisions of TSCA[69] or under the jurisdiction of other statutes, depending, among other factors, on the uses at issue. Note that if a pheromone is used in traps in conjunction with conventional pesticides, or in other application methods (other than traps), such that the exemption was no longer applicable, the pheromone would be subject to regulation under FIFRA. If the use of the pheromone was intended to control bacteria and fungi in or on living

humans or animals, it would be subject to regulation under FFDCA. To complicate this issue, whether the microbe or PBAN is considered a pesticide could well depend on which is introduced into the trap. If the microbe is used in the trap, it could likely be considered the active ingredient. If, on the other hand, the microbe is used only to produce PBAN and only the PBAN is used in the trap, PBAN would likely be the active ingredient regulated by FIFRA. In that case, the microbe could be considered a pesticide intermediate regulated by TSCA.

The legal and policy takeaway

EPA has acknowledged "that use of certain types of pheromone products presents lower risk than conventional pesticides and also acknowledges the unique properties of these niche-type products regarding their inherently narrow host range."[70] EPA's BPPD focuses on all regulatory activities associated with biopesticides, with a particular focus on registering biopesticide active ingredients and end-use products, including certain benefits available to biopesticide registration applicants, such as reduced data sets, faster review periods, and lower fees compared to conventional registrations. BPPD also implements specific programs geared towards certain biopesticides. One example is its pheromones regulatory relief program that permits, in part, flexible confidential statements of formula for pheromone experimental use permits (EUP) to allow for active ingredient adjustments during the course of experimentation.

Even with the flexibility and benefits that BPPD products have, there nevertheless remain certain challenges and complications companies must navigate through the regulatory process. As the PBAN case above demonstrates, the same substance can potentially be subject to TSCA, FIFRA, or FFDCA depending on the intent and use of the technology at issue. In addition, although EPA's policies are intended to incentivize the registration of biopesticides, the registrant still needs to generate data, seek EPA's approval for experimental testing, and otherwise provide EPA with the information it needs to assess whether the biopesticide will cause unreasonable adverse effects on human health or the environment.

Toxic Substances Control Act

The Toxic Substances Control Act (TSCA) regulates "chemical substances." Excluded from TSCA and its implementing regulations are chemicals that are regulated under other statutes, including food, drugs, cosmetics, and pesticides. TSCA was enacted in 1976 in an era of growing concern about the potential effects of chemicals in commerce on human health and the environment and the lack of regulatory oversight. Congress intended TSCA to serve as a gap-filler: if a chemical substance is not regulated under another statutory program, it is subject to TSCA.

Under TSCA's authority, EPA implements several regulatory programs related to chemical risk assessment and management, and has promulgated rules for chemical testing, recordkeeping, reporting, importing and exporting. Under TSCA Section 5, a chemical substance is "new" if it is not listed on the TSCA Inventory of Chemical Substances, EPA's master list of chemical substances in the U.S. economy that are manufactured or processed for "commercial purposes."[71] If a chemical substance is not listed on the TSCA Inventory and it is not eligible for an exemption, then it must be notified to EPA before it is manufactured in or imported into the United States for a commercial purpose. EPA is afforded a review period of not less than 90 days in which it must assess the notification and decide whether to regulate the chemical substance or allow it into the U.S. economy without restriction. There also are exemptions from the TSCA Inventory listing requirement, some of which are self-executing if the appropriate criteria are met (*e.g.*, for R&D chemicals) while others require submissions to and affirmative action by EPA.[72]

EPA interprets "manufacture for commercial purposes" broadly to mean "[t]o import, produce, or manufacture with the purpose of obtaining an immediate or eventual commercial advantage for the manufacturer."[73] As such, commercial R&D activities are subject to TSCA regulation, including certain procedural and recordkeeping requirements. By the same token, however, *noncommercial* R&D on chemical substances is not subject to TSCA. This could include, for example, academic research or that conducted by individuals as long as the activities do not meet EPA's interpretation of commercial R&D.

The Coordinated Framework provides that the U.S. Government consider microorganisms and their DNA and rDNA molecules as "chemical substances" as defined under[74] and thus subject to TSCA.[75] While this construction supported EPA's development of its TSCA Biotechnology Program, it is not without controversy. There is no explicit basis in TSCA's legislative history to suggest Congress intended to include living microorganisms within the TSCA definition of "chemical substance."[76] Chemical substance, nonetheless, is broadly defined and at their basic level, DNA molecules are chemical substances of "a particular molecular identity." As noted by one commentator, this interpretation of chemical substance "leads inevitably to the conclusion

that plants and animals (including human beings which are life forms teeming with DNA molecules) fall within TSCA's regulatory scope."[77] Regarding this last point, the "commercial purposes" requirement noted above effectively limits the scope of EPA's TSCA authority.

In its biotechnology regulations, EPA states that "new" microorganisms are those that are intergeneric and not already listed on the TSCA Inventory. The regulation defines "microorganism" as an "organism classified, using the 5-kingdom classification system of Whittacker, in the Kingdoms Monera (or Procaryotae), Protista, Fungi, and the Chlorophyta and the Rhodophyta of the Plantae, and a virus or virus-like particle."[78] An "intergeneric microorganism" is a microorganism formed by the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera.[79] An "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." It "does not include a microorganism which contains introduced genetic material consisting of only well-characterized, non-coding regulatory regions from another genus."[80] EPA states that "[m]icroorganisms that are not intergeneric are automatically included on the Inventory,"[81] because conceptually they are existing chemical substances.

EPA's implementing regulations require manufacturers of new intergeneric microorganisms for commercial purposes to submit a notification to EPA or to otherwise meet any of several available exemption procedures. EPA's "intergeneric" policy is based on traditional genetic modification techniques and the belief that the transfer of genetic information from different genera is more likely to create new or modified traits that could present a risk.[82] Commentators have noted, however, that synthetic biology raises the possibility of introducing wholly synthetic genes or gene fragments (*i.e.*, DNA sequences) that do not exist in nature into an organism and may enable scientists to remove a gene fragment from an organism, modify that fragment, and reinsert it back into the same organism. In either case, such organisms may not be "intergeneric" under EPA's definition because they would not include genetic material from organisms of different genera.[83] Non-intergeneric genetically modified microorganisms currently are not covered by any TSCA Section 5 requirements, thus raising the possibility of a large gap in the TSCA regulation of genetically modified microorganisms. Synthetic biology modifications that were not foreseen in the original regulation may have a greater probability of creating novel traits and risks than the traditional intrageneric transfers considered by EPA when it developed the regulation.

In an attempt to address preemptively the challenges of synthetic biology chemical substances, EPA states the following on its website regarding microorganisms that are the product of synthetic biology:

When defining "intergeneric microorganism," in the case of chemically synthesized genes, the Agency has followed a similar principle. The genetic sequence of the synthesized

gene may be identical to a sequence known to occur in an organism in the same genus as the recipient microorganism. If so, the resulting microorganism is considered intrageneric and thus not new. Conversely, the sequence of the synthesized gene may be different or not known to be identical to a sequence in the genus of the recipient microorganism, in which case, the resulting product is considered intergeneric. EPA strongly encourages any manufacturer of a new microorganism using synthetic DNA to contact the Agency.[84]

Thus, unless a synthetic biology manufacturer can demonstrate that the genetic sequence of the synthesized gene is identical to a sequence known to occur in an organism in the same genus as the recipient microorganism, EPA takes the position that a microorganism produced by synthetic biology is a new chemical substance subject to TSCA Section 5 requirements.

These requirements can be met in any of several ways that can involve EPA notifications or exemptions from such notifications depending on factors such as whether the activity is for R&D or for commercial use, and whether the activity is conducted in an enclosed structure or it involves environmental release. TSCA and EPA's regulations provide that a notification exemption application will not be granted unless EPA can determine that the microorganism "will not present an unreasonable risk of injury to health or the environment."[85]

In the preamble to the final rule setting forth the microorganism regulations, EPA expressed its concern about R&D activities with microorganisms because EPA believes that living microorganisms, unlike traditional chemical substances, may "reproduce and increase beyond the number initially introduced, may establish in the environment, and may spread beyond the test site."[86] Consequently, EPA provided two types of R&D exemptions for microorganisms. The first, known as a contained structure exemption, applies to R&D activities conducted with "containment and/or inactivation controls" defined as "any combination of engineering, mechanical, procedural, or biological controls designed and operated to restrict environmental release of viable microorganisms from a structure."[87] Under this exemption, certain conditions must be satisfied in addition to the general requirements for an exemption request, including, among others, that the microorganism must be manufactured, imported, or processed solely for R&D activities and not for a commercial purpose,[88] there must not be any "intentional testing of a microorganism outside of a structure,"[89] the microorganism must be used by, or directly under the supervision of, a technically qualified individual,[90] as defined in EPA's regulations,[91] and the manufacturer, importer, or processor must notify all persons in its employ or to whom it directly distributes the microorganism, that are engaged in experimentation, research, or analysis on the microorganism "of any risk to health" that may be associated with the microorganism.[92]

For R&D activities that do not qualify for the contained structure exemption, EPA requires the submission of a TERA at least 60 days

before the initiation of the proposed R&D activity. The TERA seeks information identical to the information required in a standard notification as well as detailed information on the proposed R&D activity and information on monitoring, confinement, mitigation, and emergency termination procedures.[93] Health and safety data relating to a new microorganism's health or environmental effects that are in the submitter's possession or control, however, must be submitted with the TERA.[94] The submitter must provide this information to the extent it is "known to or reasonably ascertainable by the submitter."[95] If EPA determines that the proposed R&D activity for the microorganism does not "present an unreasonable risk of injury to health or the environment," EPA will so notify the submitter and the submitter can then proceed with the proposed activity as specified in the TERA.[96] If, however, EPA concludes that it cannot determine that the R&D activity will not present such risks, EPA will deny the TERA and provide reasons for its denial in writing.[97]

For commercial activities, EPA has implemented PMN and exemption procedures. The notification is referred to as an MCAN.[98] EPA specifies in detail in its regulations the information that an MCAN must contain, including information pertinent to the microorganism's identity (including details about the genetic construction and the phenotype and ecological characteristics of the new microorganism), its intended production volumes and uses, and potential occupational or environmental exposures and releases. The submitter also must include any test data in the submitter's possession or control and describe other data known or reasonably ascertainable by the submitter concerning potential health and environmental effects of the microorganism.

Following review of the information provided in the MCAN as well as any other relevant available information, EPA can take regulatory action to restrict or ban production or uses or to require testing, if it can satisfy the "may present an unreasonable risk" regulatory threshold for issuing a Consent Order under TSCA Section 5(e). EPA can in addition or in the alternative use its authority under Section 5(a)(2) to issue a SNUR, which would require future notifications to EPA concerning "significant new uses" of the microorganism.

EPA has established a two-tiered exemption from notification requirements for commercialization of microorganisms that meet specified criteria. To qualify for the Tier I exemption: the microorganism must be one of ten species specified in the regulations; the microorganism must meet introduced genetic material criteria (*i.e.*, limited in size, well-characterized, poorly mobilizable, and free of certain toxin-encoding sequences); the physical containment and control technologies of any facility in which the microorganism will be manufactured, processed, or used must meet certain criteria; the manufacturer or importer submits a certification at least ten days prior to commencing initial manufacture or import of the new microorganism; and the manufacturer or importer complies with recordkeeping requirements.[99] The Tier II exemption provides for an expedited review of microorganisms that satisfy Tier I requirements, except for the requirement that the facility meets all necessary physical

containment and control technologies requirements.[100] Manufacturers and importers must submit to EPA a Tier II exemption application at least 45 days prior to commencing initial manufacture or import of the new microorganism.[101] EPA will approve or deny the Tier II exemption request no later than 45 days after EPA receives the request.[102]

Finally, as an alternative to filing a notification, persons who intend to manufacture or import for commercial purposes a new microorganism may submit an application for a test marketing exemption (TME).[103] EPA guidance states that test marketing activities "usually involve limited sale or distribution of a substance within a predetermined period of time to determine its competitive value when its market is uncertain."[104] EPA will either approve or deny a TME application no later than 45 days after receipt, and may impose restrictions with approval.[105] The submitter "may only proceed with test marketing activities after receipt of EPA approval."[106]

Biomining Case Study

Context

Copper has all manner of uses, from wiring and building materials to jewelry and consumer goods. Its extraction has always been an expensive, energy-intensive, and often inefficient process. Copper production is increasing globally, with most mining occurring in Chile, Peru, China, and the United States.

Conventional copper mining of low-grade ore entails draining a highly acidic solution through huge piles of crushed rock. The leachate is collected and processed to capture the copper by electroplating. This

technique requires significant energy and chemicals and leaves behind much useable copper trapped in the tailings, the low-value rock byproduct of mining. To improve the yield of copper, some mines add natural microbes to the acid solution. These organisms are extremophiles, none of which is known to be pathogenic, and is capable of existing under more extreme conditions, such as those in the acidic leachate.

Description of the new technology

To make this process more efficient, a company plans to use synthetic biology to develop microbes to extract copper more efficiently from the ore. These novel microorganisms will be designed to increase the solubility and extraction of copper from ore that, using current technology, either could not be extracted or could not be extracted by economically-justified means (*e.g.*, when requisite energy input is considered). The result is an increase in extraction efficiency for copper recovery with less loss of copper in the tailings (which would represent both an economic loss and a potential for a release into the environment). In addition to being more efficient, company officials say these novel methods are better for the environment as they reduce the amount of potentially toxic metals remaining in the tailings.

The company plans to change the microbes by modifying the genetic material to increase the microbes' efficiency in leaching specific types of low-grade ore and may seek to use the modified bacteria to recover additional copper from tailings. The leaching system occurs in a loop: Once the primary copper extraction is complete the remaining leachate is reinoculated with microbes and reintroduced at the top of an ore heap rather than being disposed and potentially contributing to environmental contamination. Because of the routine addition of new inoculant, the microbes are not engineered for maximum stability and fitness and indeed cannot survive at more neutral pH (>3). As the company looks to test and eventually use these genetically modified microbes in U.S. copper mining operations, what must they consider from a regulatory standpoint?

Discussion of the legal and procedural issues

A microbe and its DNA can be considered chemical substances subject to TSCA if either is used in a manner not excluded from TSCA (*e.g.*, as a drug or pesticide). The precise chemical identity of the synthetic gene(s) is confidential. If the genes inserted into the naturally existing, recipient organism are from organisms from the same genus as the recipient, the modified organisms can still be considered naturally occurring, therefore implicitly listed on the TSCA Inventory and no TSCA Section 5 notice would be required. If, on the other hand, the synthetic genes are not identical to a sequence that occurs in an organism in the same genus as the recipient organism or are genes from an organism of a different genus that are inserted into the recipient organism, the microbe would not be considered naturally occurring and, if not otherwise listed on the TSCA Inventory, would trigger the biotechnology reporting requirement under TSCA Section 5. Note that EPA strongly encourages *any* manufacturer of

a new microorganism using synthetic DNA to contact the agency to discuss the application (*see* http://www.epa.gov/oppt/biotech/pubs/fs-001.htm).

The company is developing the modified microbe for a commercial purpose. Based on public information, it is unclear whether the microbe is eligible for a TSCA Tier I or Tier II exemption. These exemptions permit producers of modified microbes that meet the eligibility requirements to proceed to commercial production with either a ten-day notice to EPA (Tier I) or an application with a 45-day review period (for Tier II). It is unclear whether the microbe is one of the species that is eligible for these exemptions. In addition, it is unclear whether the introduced genetic material is limited in size, well-characterized, poorly mobilizable, and free of certain toxin-encoding sequences, such that it meets these aspects of the exemptions' eligibility requirements. To the extent that the use pattern may lead to release of the microbes, albeit in well-controlled, recirculated water-based leaching systems on large metal ore piles, the use would not meet the exemptions' containment requirements, so neither the Tier I nor Tier II exemption is an option. Accordingly, if the modified microbe otherwise triggers TSCA Section 5 new chemical requirements, EPA would be of the view that the manufacturer would be required to file a Microbial Commercial Activity Notice (MCAN) with EPA at least 90 days before the first non-exempt commercial manufacture of the microbe. As an alternative, the company could submit a TSCA Experimental Release Application (TERA) which, if approved by EPA, would allow the company to conduct (R&D) field studies to obtain an enhanced scientific understanding of aspects such as the microbes' survival, migration, etc. when used in the commercial process. Such understanding could be very helpful to EPA in any subsequent review of an MCAN on the microbe.

During its review, EPA will assess the potential for risk to human health and the environment, including the potential for the microbe to survive, migrate, and out-compete other microbes in the same ecosystem; transfer genetic material with wild microbes; or be pathogenic. If EPA is satisfied that the modified microbe is not likely to pose a risk to human health and the environment, it will allow the application to be "dropped from review," meaning that EPA will take no further regulatory action and the submitter may proceed with its intended non-exempt commercial production upon the expiration of the 90-day review period. If, however, EPA identifies concerns, it has the authority to ban manufacture or import of the modified microbe or to negotiate a consent order under TSCA Section 5(e) with the submitter that typically would put in place restrictions to address the risk concern as well as testing (laboratory and/or field testing) needed to understand the microbe's risks, survival, migration, etc. EPA could also determine the need for a Significant New Use Rule (SNUR) to cap or limit the production, uses, or exposure/release to those specified in the MCAN. Of the 55 MCANs received through 2013, one was withdrawn, one was regulated through a TSCA Section 5(e) consent order, one was regulated through a rulemaking (a TSCA Section 5 SNUR), and

the remaining were allowed to proceed to market without restrictions. It is not clear from the available information how many of these MCANs involved intentional environmental release (as opposed to contained use) of the microorganism. In addition, we note that only 2 of 29 valid TERAs submitted to EPA were not approved.

The legal and regulatory takeaway

EPA is authorized under TSCA to regulate microorganisms created through synthetic biology for use in biomining. This is particularly the case when synthetic sequences are used to modify microorganisms in a way that introduces genetic sequences that are not known to be identical to those known to occur in an organism in the same genus as the recipient microorganism. Such genetically modified microbes would be considered new chemical substances subject to review under TSCA Section 5. EPA has a record of reviewing and regulating biotechnology products that is similar to its decisional record on regulating conventional chemicals:

- 95 percent of intergeneric microorganisms that have been the subject of MCANs have proceeded to commercial distribution without restriction;
- 93 percent (27 of 29 applications) of intergeneric microorganisms that have been the subject of TERAs have been approved; and
- 93 percent of conventional chemicals subject to Premanufacture Notification (PMN) have not been regulated via a Section 5(e) order or a SNUR (an additional 5 percent have been voluntarily withdrawn by the notifier, often in the face of possible EPA action).

Biomining, however, could represent a use and involve a microbial species not previously considered by EPA. These factors combined with environmental releases that, given the size of mining operations, could be considered large, environmentally consequential, and ongoing are likely to present novel issues to the TSCA biotechnology program. These complex issues have the potential to attract close EPA scrutiny that would, at a minimum, likely necessitate voluntary suspensions of the review period, delay the decisional process, and increase the likelihood that EPA would determine the need to apply testing requirements to improve its understanding of potential risk aspects and/or controls on the use. If use of a modified microorganism contributed to economic and environmental benefits (*e.g.*, greater recovery of copper, and reduced residual releases to the environment of a toxic metal), these points would be important to discuss and document in a Pollution Prevention Information page attachment to the MCAN.

Plant Protection Act

In addition to EPA and FDA authorities and activities discussed above, the Coordinated Framework relies also on the USDA, primarily through the Animal and Plant Health Inspection Service (APHIS), to carry out the third prong of the coordinated approach. APHIS is tasked with regulating field trials of genetically modified crops and plants under the Plant Protection Act (PPA), enacted in 2000.[107] The objective of the PPA is "to prevent the spread of parasitic, diseased, and invasive plants and organisms, and it does so through the regulation of 'plant pests' and 'noxious weeds.'"[108] When the Coordinated Framework originally was launched nearly 30 years ago, the relevant federal statute was the Federal Plant Pest Act, under the authority of which APHIS first issued the implementing regulations that govern its activities in regulating genetically modified plants. At that time, noxious weeds were addressed separately under the Federal Noxious Weed Act. In combining the regulatory objectives of these two earlier statutes, the PPA does not differ significantly from either of them in the aspects pertinent here.

The key term for purposes of regulating genetically modified plants and crops under the PPA is "plant pest"; unless an organism falls within the definition, it is outside the regulatory scope of the statute. A fundamental aspect of the definition is the capability of the organism at issue to injure or cause damage or disease in a plant. Thus, under the PPA definition, a "plant pest" is "[a]ny living stage of any of the following that can directly or indirectly injure, cause damage to, or cause disease in any plant or plant product:

(A) A protozoan.

(B) A nonhuman animal.

(C) A parasitic plant.

(D) A bacterium.

(E) A fungus.

(F) A virus or viroid.

(G) An infectious agent or other pathogen.

(H) Any article similar to or allied with any of the articles specified in the preceding subparagraphs."[109]

The APHIS implementing regulations at 7 C.F.R. Part 340[110] define "plant pest" similarly, as "[a]ny living stage (including active and dormant forms) of insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi, other parasitic plants or reproductive parts thereof, viruses; or any other organisms similar to or allied with any of the foregoing; or any infectious agents or substances, which 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."[111]

Certain genetically modified organisms are deemed "presumptive plant pests" and regulated as such by APHIS -- those created through the use of an organism that itself

meets the definition of "plant pest." Any of these is considered a "regulated article," defined as:

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 [7 C.F.R.] § 340.2 and meets the definition of plant pest, or is an unclassified organism and/or an organism whose classification is unknown or any product which contains such an organism, or any other organism or product altered or produced through genetic engineering which the [APHIS] Administrator determines is a plant pest or has reason to believe is a plant pest.[112]

This definition of a "regulated article" incorporates a quite broad assertion of threshold jurisdiction under the PPA, because the techniques typically used to create many genetically modified organisms may involve use of a donor organism and/or a vector agent that is included in the designated genera or taxa. A wide range of genetically modified organisms not confined to genetically modified plants would satisfy this element for APHIS jurisdiction. Nevertheless, the definition is also limited to those genetically modified organisms that otherwise satisfy the general definition of a plant pest. In practice, most genetically modified organisms that could be deemed to be a potential plant pest are genetically modified plants.

Moreover, not every genetically modified plant will be deemed to be a potential plant pest. Nothing in the PPA or in the APHIS regulations states that a genetically modified plant is a plant pest simply due to the fact of its genetic modification. The capability to cause injury, harm, or damage to a plant or product also must be present. If (and only if), however, a genetically modified plant meets the definition of a "plant pest" -- which includes that harmful capability -- it is subject to regulation by APHIS.[113]

APHIS oversees three possible pathways for using genetically modified plants (with the extent of such use to be determined). The simplest is a notification procedure available under 7 C.F.R. § 340.3 for a limited subset of plants, subject to specified criteria and performance standards; APHIS will approve or deny a notification submitted by an applicant.[114]

More elaborate is the second pathway, a field testing program under 7 C.F.R. § 340.4, which requires a body of information to be submitted to APHIS in support of an application for a field testing permit for the genetically modified organism for which testing authorization is sought.[115] An applicant may pursue a field testing permit as an initial step or may seek such a permit if APHIS denies the applicant's notification for a specific plant.[116] The regulations set out in some detail the information that must be included in a field testing permit application. A permit will be issued only if APHIS decides, based on the applicant's submission, that the testing can go forward, subject to any necessary conditions, without posing plant pest-associated risks beyond the test site. This enables APHIS, as well as the applicant, to obtain data relevant to how the presumptive plant pest affects other plants when introduced into the environment on a limited basis.[117]

Should a field test yield favorable results -- that is, if the test results, along with other relevant data, appear to make a persuasive case that the plant or plant product does not represent a plant risk -- "[a]ny person" may petition APHIS for a "determination of nonregulated status."[118] Also referred to as "deregulation," this is the third option and clears a pathway for seeking commercialization. The contents of this data-driven, substantive filing and the procedures for evaluating it -- including notice in the *Federal Register* and an opportunity for public comment, followed by a further opportunity for the petitioner to respond -- are specified in the regulations.

Before making a decision to deregulate, APHIS must comply with NEPA, which requires federal agencies to prepare an EIS if an agency action will significantly affect the environment.[119] APHIS, like other agencies, need not undertake the lengthy and often complex EIS process if the "prequel" inquiry also required by NEPA, in the form of an Environmental Assessment (EA), concludes that the proposed action will not significantly affect the environment. In such instances, the agency will issue a "Finding of No Significant Impact" (FONSI) and proceed with the proposed action without preparing the EIS.

With nearly three decades of field test permitting and evaluation of petitions to deregulate presumptive plant pests, APHIS has played a considerable role in the expanding universe of genetically modified plant products. According to the Venter Report, the number of field trials authorized by APHIS on genetically engineered plants since 1987 has run into the thousands, and 95 genetically engineered crops have been deregulated as of August 2013.[120]

APHIS also is authorized under the PPA to regulate "noxious weeds,"[121] but it has not opted, at least thus far, to use this authority to address genetically modified plants.[122] The APHIS regulations in 7 C.F.R. Part 360 -- a separate regulatory regime from the one in Part 340 addressing plant pests -- defines "noxious weed" expansively as "[a]ny 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."[123] In contrast to the Part 340 regulations for plant pests, there is no operative concept of a "presumptive" noxious weed. APHIS may assess and list a plant as a "noxious weed" on its own initiative and also will evaluate petitions to list or delist a plant. A listed plant may not be imported into or disseminated within the United States except if, and as authorized by, an APHIS-issued permit.[124]

APHIS has been criticized by advocates of broader and more careful government oversight of genetically engineered or modified products for (among other things) declining to exercise its authority to regulate noxious weeds more expansively and proactively to reach genetically modified plants. APHIS likewise has been criticized for taking narrow view of its role once it has conferred deregulated status on a formerly presumptive plant pest by approving a petition for such; APHIS consistently has taken the position that in the absence of a

plant pest, its statutory responsibility under the PPA is at an end. Its position as to what constitutes the injury, disease, or damage in plants that makes the responsible organism in the first place also falls short in the view of these advocates for enhanced regulation. This plausible, plain-meaning interpretation by APHIS is considered insufficient by those who believe that it makes better sense to read these harms to encompass wider environmental and economic harms, such as the potential for a genetically modified plant ultimately leading to increased herbicide use.

The Ninth Circuit upheld APHIS's reading of the law in 2013 in *Center for Food Safety v. Vilsack*,[125] which involved a challenge to APHIS's deregulation of "Roundup Ready Alfalfa" (RRA), a plant genetically modified to be resistant to the herbicide glyphosate, marketed as "Roundup." Roundup had proven problematic in use by alfalfa farmers to control weeds because the alfalfa crop, as well as the weeds, succumbed to the herbicide. RRA was engineered to enable the alfalfa crop to survive the application of the weed-killing Roundup. Various environmental groups and farmers have fought attempts by Monsanto and Forage Genetics International (Forage Genetics), its producers, to introduce RRA, and a long history of litigation has resulted.[126] Opponents of RRA's use have challenged aspects of APHIS's deregulation of RRA over the years, and the Ninth Circuit's 2013 decision squarely addressed and upheld APHIS's determination that RRA was not a "plant pest" within the meaning of the PPA and thus that its deregulation did not violate statutory obligations under NEPA and the Endangered Species Act (ESA), as the petitioners had alleged.[127]

In a systematic opinion that summarized the salient points of the litigation to date, the Ninth Circuit rejected the petitioners' contentions that APHIS had interpreted the meaning of "plant pest" too narrowly. The petitioners' position was that "plant pest" includes all genetically engineered plants and organisms that have an environmentally adverse effect on plants -- in this instance, the transgenic contamination of conventional alfalfa and the increased herbicide use. APHIS's position was that whether or not the harms alleged by the petitioners were adverse environmental and economic effects associated with RRA, those harms did not constitute plant disease, injury, or damage, the endpoints identified under the PPA.

The court agreed. As described in the opinion, RRA was created by transferring a gene from Agrobacterium, a naturally-occurring bacterium -- and a listed "plant pest" -- into the genetic structure of the alfalfa plant. The effect of inserting this gene was to alter the genetic structure of the alfalfa plant to make it resistant to glyphosate (Roundup). The presence of Agrobacterium on the list of plant pests meant that APHIS considered RRA as a presumptive plant pest, triggering restrictions on its use. After Monsanto and Forage Genetics applied to deregulate RRA, APHIS's review of the submitted data and the public comments led it to determine that the plant pest properties of the Agrobacterium used to engineer RRA was "disarmed" and could not injure or damage other plants and presented no greater plant pest harms than conventional alfalfa. APHIS granted the application and unconditionally deregulated RRA.[128]

The Ninth Circuit acknowledged the petitioners' assertions of potential environmental and economic harm from the use of RRA (distinguishing between RRA itself and its use), but it agreed with APHIS that such potential harms were outside the scope of the PPA. According to the court, "the PPA addresses only the harms caused by plant pests to other plants and APHIS can regulate RRA only if it causes plant pest harms."[129] Observing that "[t]he PPA was enacted to protect plants, but not to control the burgeoning use of chemicals in crop production," the court refused to "interpret the language of the PPA, which Congress has not materially amended since 1957, to address the alleged harms that may result from the modification of the plant's genome."[130] If the law was to be updated, it was a job for Congress, not the court. Thus, the court ruled that RRA is not a plant pest within the meaning of the PPA. The court addressed and disposed of, as well, the petitioners' remaining theories as to why the deregulation should not stand, including the theory that in evaluating the application to deregulate RRA, APHIS was required to determine also whether RRA was a "noxious weed" under the separate regulatory framework for addressing them.[131]

By putting the task of updating or supplementing the PPA to address 21st century concerns squarely in the lap of Congress, *Center for Food Safety v. Vilsack* underscores some of the reasons why the PPA in its present form could be considered an imperfect tool for regulating genetically engineered plants and plant products. It is fair to predict that Congress is unlikely to undertake any near-term steps to update this element of the laws addressed under the Coordinated Framework and that regulation -- and deregulation -- will proceed under generally the same procedures and rules for the foreseeable future.[132]

With new statutory tools for addressing the challenges of genetically modified plants unlikely to materialize in the near-term, the impatience of many critics about APHIS's reluctance to be more proactive may have some merit. One key task of USDA is to promote domestic agriculture, and significant differences will persist among different constituencies about how this end best can be accomplished. Opponents of genetically modified plants and plant products will continue to paint APHIS as weak in fulfilling its role as gatekeeper and as overly inclined to "promote agriculture" through deregulation of what these opponents view as harmful innovations.[133] At the same time, the requirements of the APHIS regulations are viewed as burdensome enough by many prospective developers of genetically modified plants to incentivize these developers to try to bypass the regulatory regime insofar as possible by pursuing genetic modifications that do not make use of an identified "plant pest" in the first place.[134] Where the regulatory hook provided by the presence of a plant pest is absent -- where the genetic modification technique does not employ a plant pest -- APHIS has concluded that it must stand aside in these instances.[135] Accordingly, as genetic modification techniques become increasingly sophisticated, the numbers of plants and products outside the reach of APHIS's

authority can be expected to expand, even as APHIS will continue to play a critical role where plant pests are involved.

New techniques employ technologies that are confounding the application of traditional oversight authorities. For example, "genome editing" occurs when foreign genetic material comes exclusively from other plants and is embedded with a gene gun and not through a bacterium. By avoiding the use of a plant pest, arguably the authority of federal laws is side-stepped. As the *New York Times* pointed out, "companies can get around the oversight by avoiding components for plant pests."[136]

Genetically Modified Plant Case Study

Context

Ornamental plants have been used for centuries to add aesthetic appeal to outdoor and indoor spaces. They are valued for their flowers, leaves, scents, texture, fruit, stem, and bark -- or simply their unique aesthetic forms. Ornamental plants have been bred to accentuate desirable traits and minimize undesirable ones through traditional cross-breeding, grafting, and other techniques.

Description of the new technology

With the advent of synthetic biology, there are new opportunities to modify ornamental plants in ways that were not available through traditional techniques. Examples include novelty plants that are bioluminescent and glow in the dark and lawn grasses that require less mowing and are deeper green in color.

Bioluminescent plants are being developed by two companies and each effort provides an instructive example of evolving technologies. Scientists at BioGlow LLC (BioGlow)[137] inserted genes from luminous marine bacteria into *Nicotiana alata* (jasmine tobacco), a common flowering ornamental plant. They have produced a plant that is autoluminescent, meaning it glows in the dark with only standard plant nutrients. BioGlow's plants have been commercialized and the company opened a web store in September 2014 (http://bioglow.us/blogs/news); as of July 2015, the Biobulb™ is listed for sale in the store (http://bioglow.us/collections/glowing-plants-2).

Glowing Plant, Inc. (Glowing Plant),[138] a company funded through a Kickstarter[139] campaign, also developed a luminescent plant. Building on technology similar to BioGlow's, Glowing Plant has inserted genetic material into *Arabidopsis thaliana* (thale cress) using a "gene gun." Genes from *Photinus pyralis* (common eastern firefly) and two synthetic variants of genes from *Aequorea victoria* (crystal jelly) are inserted into the plant's genome.

A January 1, 2015, *New York Times* article describes commercial efforts to develop genetically modified grass that requires less mowing, is deeper green in color, and is resistant to damage by the herbicide glyphosate.[140] According to the article, the manufacturer introduces genetic material from other plants that are not considered plant pests and inserts the genes with a gene gun. Publicly available information[141] suggests that *Arabidopsis thaliana* is the source of the glyphosate resistance, but does not disclose the source of the donated genetic material for the color, thickness, and height properties.[142]

These are three examples of a burgeoning market in which companies are seeking to use modern synthetic biology and genetic technologies to develop ornamental plants with desirable characteristics. The source of genetic material and the manner by which it is introduced into the host plant control how these organisms are regulated -- or not -- as discussed below.

Discussion of the legal and procedural issues

The USDA's APHIS jurisdiction to regulate genetically modified plants depends on the use of a plant pest as part of the genetic engineering technique. Until recently, use of a plant pest as part of genetic engineering was a common practice. If, however, the donor organism, recipient organism, vector, or vector agent does not meet the PPA definition of a plant pest, then APHIS' position is that it does not have regulatory authority over the modified plant. As gene guns and other new synthetic biology techniques typically do not rely on plant pests, plants modified through these techniques will not be subject to APHIS' review. If either the gene donor or recipient species is a plant pest, or if a plant pest, such as an agrobacterium, is used to introduce the genetic material into the host, the PPA will apply and APHIS will retain regulatory oversight.

BioGlow submitted to APHIS the information pertinent to support a regulatory review. Following its review, APHIS concluded in a

March 21, 2013, letter that it did not have regulatory jurisdiction over the plants, stating:

> APHIS has determined the plants, as described in the letter, are not plant pests, no organisms used as sources of the genetic material to create the plants are plant pests, and the method used to genetically engineer the plants did not involve plant pests.[143]

BioGlow's APHIS application protects the details of the genetic modification so, unfortunately, the genetic source of the bioluminescence and the method used to modify the jasmine tobacco cannot be evaluated here.

The Glowing Plant luminescent plant uses no genetic material from a plant pest, does not use a plant pest as a recipient organism, and no plant pest is used to modify the genes of the host plant. Based on these facts, APHIS reached a conclusion similar to BioGlow's in a letter to Glowing Plant dated December 23, 2014:

> No plant pests, unclassified organisms, or organisms whose classification is unknown are being used to genetically engineer this plant. In addition, APHIS has no reason to believe that this plant is a plant pest. Therefore APHIS does not consider the [genetically engineered (GE)] plant as described in your October 1, 2014 letter to be regulated under 7 CFR part 340.[144]

Glowing Plant is an open-source technology and the developers encourage others to further modify the genome of the plant. If others modify the genome of the Glowing Plant, re-submitting notice to APHIS is likely prudent, to confirm that the revised genome similarly is unregulated. As APHIS points out in its response letter:

> APHIS' response that follows evaluated your request for this plant species only and the transformation, genes and donors used to produce this specific plant line, therefore, this response is not considered relevant to other plant species, transformation, donors, or genetic material.[145]

Glowing Plant was funded through Kickstarter and offered inducements at a variety of funding levels, which raise separate regulatory issues. Pledges at the $150 level will receive a glowing plant, which as discussed above does not appear to be regulated, at least not by APHIS under the PPA. Pledges of $250, however, receive a "DIY MAKER KIT," which includes "a full set of instructions and all the ingredients you need to transform your own plant at home, in your lab or at school." Two notable issues are raised by the DIY kit. First, the DIY kits employ agrobacterium to perform the genetic modification on plants. Agrobacterium is regulated as a plant pest. Consequently, while the Glowing Plant modified by a gene gun may not be regulated under the PPA, the agrobacterium DIY kit is likely regulated, either under PPA or TSCA. Second, the supporter who receives the kit appears to be legally responsible for obtaining a permit from APHIS for plants they transform. Given the likely lack of regulatory sophistication of the typical Kickstarter supporter, there is a significant opportunity for someone unknowingly to violate one of the statutes that regulate genetically modified plants.

Pledges at the $500 level receive a message (up to 140 characters of the donor's choice) encoded in a string of single-stranded, synthetic DNA using Craig Venter's ASCII-to-DNA translation table. Even though the amounts of DNA produced in this way were exceedingly small, just a few micrograms, their manufacture is regulated by TSCA and the company was required to notify EPA prior to manufacturing the DNA strands. Glowing Plant opted to file a low-volume exemption for each of the message strings ordered by its eligible donors.

The legal and regulatory takeaway

Whether these plants pose any risks to human health or the environment is unclear. Gaps in federal oversight of such products, however, allow their market entry absent an assessment of potential risk other than simply the presence of plant pests or plant pest genes. Whether these plants may out-compete other plants in the ecosystem into which they are introduced, have an adverse effect on an animal that may consume them, or generate allergens, are among the issues that have not been comprehensively examined under current legal authorities. It is not clear that modern synthetic biology techniques raise greater risk issues than traditional cross breeding, grafting, or irradiation techniques that have been used for decades -- or even centuries. These techniques have, in many cases, escaped regulatory scrutiny, but also have not introduced substantial identified risks. It would appear, however, that modern synthetic biology allows a greater range of genetic combinations at a faster pace than previous techniques, thereby meriting a conversation about whether pre-market review is warranted. To respond to this increased pace and ability to modify plants, APHIS has been attempting to update the regulations governing genetically modified organisms under its purview. APHIS proposed a rule in 2008 and received 88,000 comments.[146] After suggesting it would proceed with a final rulemaking, APHIS formally abandoned that effort on March 4, 2015.[147] The Service announced it would restart discussions on modernizing genetically modified organism regulations, starting with "an open and robust policy dialogue to drive the development of a forward-looking rule that will provide a foundation for our future regulatory activities."[148] In its communication withdrawing the rule, APHIS stated "current regulations have been effective in ensuring the safe introduction of GE organisms," adding that "revising our biotechnology regulations will better position us to address new challenges, as well as meet current needs in evaluating and addressing the plant pest or noxious weed risks associated with the importation, interstate movement, and field release of certain GE organisms." This text has since been removed from APHIS's website.

APPENDIX: NATIONAL ENVIRONMENTAL POLICY ACT

Introduction

The most venerable of the modern environmental statutes, the National Environmental Policy Act (NEPA),[149] is sweeping on its face. It "establishes a 'national policy [to] encourage productive and enjoyable harmony between man and his environment,' and was intended to reduce or eliminate environmental damage and to promote 'the understanding of the ecological systems and natural resources important to' the United States."[150] NEPA requires federal agencies to incorporate environmental considerations in their planning and decision-making through a systematic interdisciplinary approach. It obligates all federal agencies to describe in detail and assess the anticipated impacts of all "Federal actions significantly affecting the quality of human environment."[151] This is the EIS.

Specifically, the EIS mandate in NEPA Section 102(2) directs all federal agencies to:

> (C) include in every recommendation or report on proposals for legislation and other major Federal actions significantly affecting the quality of the human environment, a detailed statement by the responsible official on—
>
> (i) the environmental impact of the proposed action,
>
> (ii) any adverse environmental effects which cannot be avoided should the proposal be implemented,
>
> (iii) alternatives to the proposed action,
>
> (iv the relationship between local short-term uses of man's environment and the maintenance and enhancement of long-term productivity, and
>
> (v) any irreversible and irretrievable commitments of resources which would be involved in the proposed action should it be implemented.[152]

The EIS requirement, enacted at the dawn of the modern era of federal environmental legislation, was intended to assure that concerns that earlier might have been overlooked or consigned to the fringes now would be part of the conversation, at least where the federal government played a role in initiating, approving, or funding an activity. Thus, the EIS itself was meant "to provide full and fair discussion of significant environmental impacts and [to] inform decisionmakers and the public of the reasonable alternatives which would avoid or minimize adverse impacts or enhance the quality of the human environment."[153] At the same time, NEPA was not intended to put a finger on the scale, as opposed to creating a process for consideration. It does not mandate any given outcome. Instead, it "imposes only procedural requirements on

federal agencies with a particular focus on requiring agencies to undertake analyses of the environmental impact of their proposals and actions."[154]

In the decades since NEPA was enacted, preparation of an EIS has proven frequently to be a substantial and time-consuming undertaking. It can be an expensive one as well, and not only in terms of government resources; where a private party is seeking a federal approval, the private entity likely will do much of the heavy-lifting, retaining expert consultants in the area of interest to survey, test, analyze, report, and so forth, with the work product provided to the relevant government agency as raw material for its development of the EIS. Public participation and the involvement of stakeholders add time and complexity to the process. In some instances, an EIS -- or the absence of one -- ends up in litigation. Opponents of major projects of all kinds have come to rely on the EIS process as a potentially powerful instrument of delay and a weapon of attrition, even where a clear-cut win is unlikely.

NEPA Review in the Synthetic Biology Context

What NEPA can contribute to a federal regulatory structure for synthetic biology has its limits, for two reasons. First, as noted above, federal agencies are not compelled to treat the results of an environmental impact analysis as a driving factor in decision-making; even where environmental impacts are carefully evaluated, the law does not compel that they trump the other factors relevant to the determination of whether, and under what conditions, a "major Federal action" will go forward. Additionally, as discussed below, decision-makers are authorized under NEPA's implementing regulations, where the situation warrants, to truncate their environmental review process before it reaches the EIS preparation stage.

The second limitation is specific to EPA in its role of implementing the various federal environmental statutes that it is charged to administer. For most of the latter purposes, EPA is exempt from NEPA, either because of an explicit exemption written into the statute itself or because the case law over the years has acknowledged and validated a "functional equivalence doctrine" for EPA's activities. The rationale is that since EPA's mission is protection of the environment, a rigid step-by-step compliance with the formalities of NEPA in the course of its activities is unnecessary, assuming that EPA provide opportunities for public participation in a given decision-making process and also considers the public comments in assessing the substantive environmental factors relevant to the decision. For purposes of regulating synthetic biology under existing laws, this means that NEPA does not apply in connection with EPA's administration of FIFRA or TSCA. As described below, however, NEPA comes into play in the implementation of both the PPA by APHIS and the FFDCA by the FDA.

For purposes of government-wide oversight and implementation, NEPA established a CEQ, which promulgates regulations that are binding on federal agencies.[155] Among other things, the CEQ regulations specify a process for determining whether an EIS is necessary in the first instance. Some

actions may be "categorically excluded" from detailed environmental review if they satisfy specified criteria that an agency has determined previously are indicative that no significant environmental impact will ensue.[156] Specific listings of such categorical exclusions are found in an individual agency's NEPA regulations. For most actions -- those that are not categorically excluded -- the CEQ regulations call on the federal agency to prepare a written EA to determine whether or not a contemplated action would significantly affect the environment.[157] Absent a "significant impact" finding, the agency need not proceed to the EIS preparation stage and instead will issue a FONSI, which may or may not include mitigation measures as needed.

A. Animal and Plant Health Inspection Service (APHIS)

APHIS regulations implementing NEPA are found at 7 C.F.R. Part 372. The regulations classify agency actions by the level of NEPA review they necessitate -- actions normally requiring an EIS, under Section 372.5(a); actions normally requiring an EA but not necessarily an EIS, under Section 372.5(b); and actions excluded categorically, under Section 372.5(c). The regulations also specify exceptions for the categorically excluded actions -- essentially an override provision -- directing that an EIS or an EA is to be prepared if the decision-maker determines that a categorically excluded action may have the potential to affect significantly the quality of the human environment.

Under Section 372.5(a), APHIS actions normally requiring an EIS encompass a "class of policymakings and rulemakings" that seeks generally to "establish programmatic approaches to animal and plant health issues." This provision makes no specific reference to genetically engineered species or, for that matter, to any other potential "plant health issues." Genetically engineered plants are referenced in Section 372.5(b), which lists actions normally requiring an EA, but not necessarily an EIS; these include, in (b)(4), "[a]pprovals and issuance of permits for proposals involving genetically engineered or nonindigenous species, except for actions that are categorically excluded, as provided in paragraph [372.5(c)] . . ." The class of categorically excluded actions, APHIS states in the regulations, shares many of the same characteristics as the class that normally requires an EA (but not necessarily an EIS), the major difference being that "the means through which adverse environmental impacts may be avoided or minimized have actually been built right into the actions themselves." Among the excluded actions, under the "licensing and permitting" subheading, is "[p]ermitting, or acknowledgement of notifications for, confined field releases of genetically engineered organisms and products."[158]

Under these latter provisions, therefore, neither notifications nor field test permitting for genetically modified organisms require either an EA or an EIS as a prerequisite.[159] Under Section 372.5(b)(4), the approval by APHIS of a petition to deregulate a genetically modified organism as a "plant pest" requires an EA.

As the regulations indicate, in-depth NEPA review is considered unnecessary for most APHIS activities involving genetically modified organism plants. APHIS handles notification and field test permitting without

reference to an EA, although field test permit applications must be supported by a body of data specified in 7 C.F.R. § 340.4. Some stakeholders and other observers are increasingly critical of what they perceive as insufficient attention by APHIS to the range of environmental impacts from a proliferating group of genetically engineered plant species and insufficient rigor in addressing them.

When an applicant petitions APHIS for nonregulated status for a genetically modified organism plant that otherwise would be considered a presumptive "plant pest," APHIS typically will conduct an EA under Section 372.5(b)(4). It will almost never undertake a full EIS unless the outcome of litigation compels it to do so. It is fair to say that APHIS does not envision its mission as delving deeply or widely into an exploration of potential environmental impacts of genetically modified organism plantings. It also is fair to say that APHIS's position on environmental review harmonizes with its reading of the PPA, a reading endorsed by the Ninth Circuit in *Center for Food Safety v. Vilsack*,[160] discussed above, part of the multi-pronged Roundup Ready alfalfa (RRA) litigation.

Briefly, the Ninth Circuit held that the PPA authorizes APHIS to regulate only "plant pest" harms -- disease, damage, or injury to other plants -- and not any corollary environmental or economic harms that might accompany the cultivation of a genetically modified organism plant. Further, the court agreed that once APHIS has determined that a particular genetically modified organism plant is not a "plant pest" within the meaning of the PPA, deregulating that plant is a nondiscretionary action and one to which APHIS cannot attach conditions of use. Under this reading of the law -- even though an EIS for RRA had been ordered in an earlier phase of the litigation and then prepared by APHIS -- the extent to which the EIS realistically could inform APHIS's decision-making as to deregulation was limited by the PPA itself.

Long before the 2013 *Center for Food Safety v. Vilsack* decision, NEPA issues had emerged in the protracted battle over APHIS's deregulation of RRA. Some of these issues ultimately ended up before the Supreme Court, which decided them in 2010 in *Monsanto Co. v. Geertson Seed Farms*.[161] The plaintiff farmers and environmental groups had sued APHIS in federal district court in 2005, alleging violations of the PPA, NEPA, and the Endangered Species Act. The district court ruled that APHIS had violated NEPA by failing to prepare an EIS prior to deregulating RRA, holding that an EIS should have addressed the environmental effects of weeds becoming resistant to the pesticide glyphosate and of transgenic contamination on organic farmers raising conventional alfalfa. The district court vacated APHIS's deregulation of RRA until the necessary EIS was prepared, enjoining APHIS from deregulating RRA in any aspect or allowing any subsequent planting of RRA until the EIS was completed. The court did not reach the PPA or ESA issues the plaintiffs had raised.[162] The Ninth Circuit affirmed on the NEPA issues.[163]

The Supreme Court granted certiorari and reversed the decisions below. As no party had challenged the district court's finding that APHIS had violated NEPA, the Court assumed without deciding that the district

court acted properly in vacating APHIS's decision to deregulate RRA. But -- in a victory for both Monsanto and APHIS -- the Court held that the injunctive relief ordered by the district court had gone too far in prohibiting APHIS from partially regulating RRA while it prepared the EIS. The Court emphasized that a NEPA violation in and of itself does not necessarily justify injunctive relief and that a party seeking relief under NEPA must satisfy the traditional four-factor test for issuance of an injunction.[164] In this instance, the Court held, none of those factors supported the wholesale injunction the district court had ordered. According to the Court, the injunction was so broad that it essentially preempted APHIS's authority to decide whether or not a partial deregulation would represent an unacceptable risk of environmental harm.[165] Likewise, the Court held the district court erred in enjoining on a nationwide basis any planting of RRA until APHIS had completed the EIS, irrespective of whether a partial deregulation order might issue in the interim.

APHIS released its final EIS in December 2010, at which point the district court's order vacating the earlier deregulation expired, because preparation of the EIS met APHIS's NEPA obligations. The final EIS listed two "preferred" alternatives -- partial deregulation and unconditional regulation. Although the final EIS characterized continuing regulation of RRA as the environmentally preferable of these two alternatives, APHIS concluded that unconditionally deregulating RRA was the alternative consistent with the agency's limited statutory mandate. This conclusion followed, in turn, from APHIS's earlier determination that RRA was not a "plant pest" under the PPA. As such, APHIS's regulatory authority over RRA was at an end, a reading that the Ninth Circuit affirmed.[166]

The long saga of EIS preparation and NEPA compliance in the context of the RRA deregulation underscores the extent to which the PPA limits the elevation of environmental considerations in APHIS decision-making, assuming that APHIS itself desired to give such environmental factors more weight in its regulatory choices. The order to prepare an EIS provided more information to APHIS, stakeholders, and the public -- and it delayed the deregulation of RRA by some five years -- but it did not change the ultimate outcome.

Various litigations similarly accompanied APHIS's original decision to deregulate Roundup Ready sugar beets (RRSB) in 2005, after APHIS had determined, based on an EA, that RRSBs were not a plant pest risk. As with RRA, the original deregulation was vacated and APHIS was required to prepare an EIS for RRSBs, which eventually was granted deregulated status in 2012. While the EIS was in preparation, four seed companies obtained permits from APHIS to plant juvenile sugar beet "stecklings" on limited acreage in geographically defined locations; each permit was accompanied by a NEPA "Decision Worksheet" to the effect that the steckling growth would have no significant environmental impacts. After a district court issued a preliminary injunction and ordered destruction of the stecklings, the Ninth Circuit overturned the injunction in a decision informed by the Supreme Court's opinion in *Monsanto v. Geertson Seed Farms*.[167] Quoting the Court's "warning against granting injunctive relief where APHIS's action is 'sufficiently limited' that 'the

risk of gene flow to [Plaintiffs'] crops could be virtually nonexistent,'" the Ninth Circuit ruled that the plaintiffs had failed to show the likelihood of irreparable harm necessary for injunctive relief and that the district court had abused its discretion in ordering the plants' destruction:Plaintiffs have not demonstrated that the permitted steckling plants present a possibility, much less a likelihood, of genetic contamination or other irreparable harm. The undisputed evidence indicates that the stecklings pose a negligible risk of genetic contamination, as the juvenile plants are biologically incapable of flowering or cross-pollinating before February 28, 2011, when the permits expire.[168]

The Ninth Circuit emphasized that the record revealed no examples of contamination by pollination under the restricted conditions that the permit imposed on the limited plantings: "To the contrary, APHIS has permitted over 100 confined field releases of Roundup Ready sugar beets with no known 'loss of confinement,' as the agency explained in NEPA documents issued with each permit. Plaintiffs give us little reason not to defer to APHIS's technical expertise and judgments on this score."[169] Deference to the implementing agency -- here, APHIS -- is a theme in both of the Ninth Circuit opinions discussed here, as well as in the Supreme Court decision relating to genetically engineered plants. Although challengers have succeeded in obtaining court orders requiring APHIS to prepare an EIS for controversial deregulation decisions, judicial deference to agency decision-makers magnifies the burden on those who challenge APHIS's reading of the PPA or its ultimate determination to deregulate a genetically engineered species once it has satisfied NEPA's procedural requirements.

B. Federal Food, Drug, and Cosmetic Act (FFDCA)

As regulation of products of synthetic biology under FFDCA is evolving, so are questions about the role of NEPA review in the process. The FDA regulations on environmental impact consideration are found at 21 C.F.R. Part 25. Under 21 C.F.R. § 25.15(a), all applications or petitions requesting FDA action require the submission of an EA or a claim of categorical exclusion. As prescribed by the CEQ, the EA "serves to provide sufficient evidence and analysis for an agency to determine whether to prepare an EIS or a FONSI."[170]

For FDA actions under FFDCA, preparation of an EIS is the exception rather than the rule. According to Section 25.22(a), "[t]here are no categories of agency actions that routinely significantly affect the quality of the human environment and that therefore ordinarily require the preparation of an EIS." An EIS is required only if review of an EA leads the responsible official to conclude, pursuant to the statutory language of NEPA, that "a proposed action may significantly affect the quality of the human environment."[171]

Section 25.20 lists the categories of FDA actions for which an EA must be prepared, unless categorically excluded under Sections 25.30-25.34.[172] The applicant typically is required to prepare the EA and make any corrections that may be necessary.[173] Neither the regulations on actions necessitating an EA nor those setting out the various categorical exclusions from the EA preparation requirement specifically reference products of genetic engineering, as do the

APHIS regulations previously discussed. The FDA has made it clear, however, that the EA requirement applies to certain approvals relating to the products of synthetic biology.

Where FDA's pre-market oversight, if any, is voluntary, the NEPA review is not required, whether or not the product created or derived is through genetic engineering. Where pre-market approval is mandatory, as for new human drugs or new animal drugs (NAD), an EA is necessary except where categorically excluded.[174] The regulatory status, and hence the NEPA status, of substances added to food is not uniform. Those that are classified as "food additives" require pre-market approval as to their safety, whereas other substances added to food classified as "generally recognized as safe" (GRAS) and do not need to undergo the FDA's pre-market approval process. Approval of food additive petitions is subject to the EA requirement.[175]

FDA specifically addressed its regulatory approach to foods derived from genetically modified organisms in a policy statement issued in 1992, stating that most foods derived from genetically modified plants would be presumptively GRAS, like foods derived from conventional plants. By contrast, a product "that differs significantly in structure, function, or composition from substances found currently in food" would be treated as a food additive, subject to pre-market approval and preparation of an EA.[176]

As discussed FDA regulates genetically engineered animals as NADs, and it has prepared guidance specifically addressing this area of activity. NADs generally are not considered safe unless FDA has reviewed and approved a NADA (New Animal Drug Application) for the use involved.[177] Thus, a NADA typically must be submitted for a genetically engineered animal; FDA's proposed approval of a NADA is subject to an EA requirement under 21 C.F.R. § 25.20(m), unless categorically excluded. Each applicant for an NAD approval must submit either an EA or a claim for categorical exclusion.[178]

FDA's guidance on its regulation of genetically engineered animals confirms that environmental review requirements for conventional NADAs also apply to them. According to the guidance document:

An EA that demonstrates the GE animal will not significantly affect the quality of the human environment leads to a finding of no significant impact (FONSI). We recommend that the EA focus on environmental issues and potential impacts related to the use and disposal of the GE animal and its final product, if relevant. The appropriate scope and content of the EA may vary widely depending on the GE animal product, claim, and conditions of use.[179]

FDA, as discussed in its GE Guidance, provides for certain exceptions to the EA requirement for genetically engineered animals. Although all genetically engineered animals are subject to FDA's pre-market approval, FDA may opt in some cases to exercise enforcement discretion, in which instances NEPA review will not occur. A categorical exclusion from the EA requirement for investigational studies on some genetically engineered animals also may be available.[180]

The issue whether an agency approval for a synthetic biology product requires an EIS and

the extent to which activities must be limited while the EIS is being prepared, has not been aired extensively through litigation for FFDCA approvals, as they have been for PPA approvals. If and when this occurs, as more such products fall within FDA's jurisdiction, NEPA review in the FFDCA context will be fleshed out further. Additionally, as needs and circumstances change, FDA may determine to issue further guidance and/or to revise its environmental review regulations accordingly.

ENDNOTES

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4 Widmaier DM, Tullman-Ercek D, Mirsky EA, Hill R, Govindarajan S, Minshull J, Voigt CA, *Engineering the Salmonella type III secretion system to export spider silk monomers*, *Mol Syst Biol*. 5:309, 2009.

5 Presidential Commission Report at 57.

6 Presidential Commission Report at 71.

7 *Id.*

8 51 Fed. Reg. 23302 (June 26, 1986).

9 NIH, Office of Science Policy, Office of Biotechnology Activities, *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (Nov. 2013), available at http://oba.od.nih.gov/rdna/nih_guidelines-oba.html.

10 *Id.*

11 According to the Friends of the Earth, International Center for Technology Assessment, and the ETC Group's "*Principles for the Oversight of Synthetic Biology*," the Precautionary Principle must be applied to synthetic biology because the risk of the technology is inherently unpredictable with potentially far-reaching and irreversible impacts. Applying the Precautionary Principle to the field of synthetic biology first necessitates a moratorium on the release and commercial use of synthetic organisms, cells, or genomes until government bodies, with full participation of the public, have: developed a research agenda guided by the public interest; ensured that alternative approaches to synthetic biology applications have fully been considered; conducted full and inclusive assessments of the implications of this technology, including but not limited to devising a comprehensive means of assessing the human health, environmental, and socio-economic impacts of synthetic biology and preventing harms where they are present; and developed national and international oversight and security mechanisms equipped to keep pace with the risks as synthetic biology technologies develop. Principles at 3, available at http://www.foe.

org/news/archives/2012-03-global-coalition-calls-oversight-synthetic-biology.

12 FDA, Strategic Priorities: 2014-1018 (Sept. 2014) at 2, available at http://www.fda.gov/aboutfda/reportsmanualsforms/reports/ucm227527.htm.

13 An exploration of the differences with respect to how products are approved for use under FFDCA requires a detailed analysis of specific commercial products that is beyond the scope of this paper.

14 J. Paradise and E. Fitzpatrick, "Does Re-Writing Nature Require Re-Writing Regulation?," *Penn. State Law Review,* Vol. 117, at 53 (Paradise and Fitzpatrick).

15 S. Carter, M. Rodemeyer, M. Garfinkel, and R. Friedman, *Synthetic Biology and the U.S. Biotechnology Regulatory System: Challenges and Options*, J. Craig Venter Institute (Venter Report) (May 2014) at 18-22 (Venter Report), available at www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-biology-and-the-us-regulatory-system/full-report.pdf.

16 Under NEPA, federal agencies engaged in "major Federal actions significantly affecting the quality of the human environment" must prepare detailed statements assessing the environmental impact of and alternatives to such actions. NEPA § 102(2)(C), 42 U.S.C. § 4332(2)(C).

17 For example, Bovine somatotrophin (BST), also known as bovine growth hormone (BGH), was developed in the 1970s, submitted for approval to FDA and ultimately approved by the agency for use in feed animals in 1993.

18 FFDCA § 201(g)(1), 21 U.S.C. § 321(g)(1).

19 Section 351 of the Public Health Service (PHS) Act defines a biological product as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, … applicable to the prevention, treatment, or cure of a disease or condition of human beings." PHS Act § 351, 42 U.S.C. § 262. Note that biological products subject to the PHS Act also meet the definition of drugs under the FFDCA. Accordingly, products such as insulin, glucagon, and growth hormone are regulated by FDA as drugs.

20 The enhancement of FDA's post-approval regulatory authority was an impetus for the Food and Drug Administration Amendments Act of 2007 (FDAAA).

21 Paradise and Fitzpatrick at 69.

22 *Id*.

23 *Id*. at 69-70.

24 FDA, *Guidance for Industry: Safety of Nanomaterials in Cosmetic Products.* (Guidance on Nanomaterials in Cosmetics), available at http://www.fda.gov/Cosmetics/GuidanceRegulation/GuidanceDocuments/ucm300886.htm; FDA, *Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives*" (Guidance on Effects of Emerging Technologies on Food Ingredients and Food Contact Substances), available at http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm300661.htm.

25 Guidance on Effects of *Emerging* Technologies on Food Ingredients and Food Contact Substances at 7.

26 "Cosmetic" is defined in FFDCA § 201(i), 21 U.S.C. § 321(i), as "(1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that the term shall not include soap."

27 CDC, *Dengue Homepage: Entomology & Ecology*, available at http://www.cdc.gov/dengue/entomologyecology/.

28 Florida Keys Mosquito Control District, *Questions and Answers on GM Mosquitoes*, available at http://keysmosquito.org/question-answers-on-gm-mosquitoes/.

29 Oxitec, available at http://www.oxitec.com/.

30 H.K. Phuc, *et al.* (2007). "Late-Acting Dominant Lethal Genetic Systems and Mosquito Control," *BMC Biology* 5:11.

31 Oxitec, *How the Self-Limiting Gene Works*, available at http://www.oxitec.com/ridl-science/understanding-ridl-science/molecular-biology/.

32 FFDCA § 201(g)(1), 21 U.S.C. § 321(g)(1).

33 CVM (2009), *Guidance for Industry Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs* (GFI 187), available at http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf.

34 FDA (2003), *Statement Regarding Glofish*, available at http://www.fda.gov/animalveterinary/developmentapprovalprocess/geneticengineering/geneticallyengineeredanimals/ucm413959.htm.

35 NEPA § 102(2)(C), 42 U.S.C. § 4332(2)(C).

36 FOE, *Issue Brief: Genetically Engineered Mosquitoes in the U.S.*, at 3, available at http://libcloud.s3.amazonaws.com/93/df/1/959/5/Issue_brief_GE_mosquitoes_in_U.S.pdf.

37 *Id.*

38 21 U.S.C. §§ 360ccc(a)(3)(A) and 360ccc-1(a)(2).

39 FDA, *ADUFA*, available at http://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/default.htm.

40 21 C.F.R. § 514.1(b)(5).

41 GFI 187 at 17.

42 FDA, *From an Idea to the Marketplace: The Journey of an Animal Drug through the Approval Process*, available at http://www.fda.gov/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm219207.htm.

43 Cosmetic Ingredient Review accessed at http://www.cir-safety.org/ingredients.

44 U.S. Fish and Wildlife Service's endangered and threatened species list is accessible at http://ecos.fws.gov/speciesProfile/profile/speciesProfile?spcode=E0CL.

45 Stephanie Strom, *Companies Quietly Apply Biofuel Tools to Household Products*, *The* N.Y. Times, May 30, 2014, accessed at http://www.nytimes.com/2014/05/31/business/biofuel-tools-applied-to-household-soaps.html?_r=0.

46 Amyris, accessed at https://amyris.com/innovation/industrial-production/.

47 FFDCA § 201(i), 21 U.S.C. § 321(i).

48 FDA, *Is It a Cosmetic, a Drug, or Both? (Or Is It Soap?)*, available at http://www.fda.gov/Cosmetics/GuidanceRegulation/LawsRegulations/ucm074201.htm#Definecosmetic.

49 For example, bithional, chlorofluorocarbon propellants, methylene chloride, and vinyl chloride, among others, are prohibited for use as cosmetic ingredients. *See* 21 C.F.R. §§ 700.11-700.35.

50 FDA, *Draft Guidance for Industry: Cosmetic Good Manufacturing Practices* (Feb. 12, 1997; revised Apr. 24, 2008, and June 2013), available at http://www.fda.gov/Cosmetics/GuidanceRegulation/GuidanceDocuments/ucm353046.htm.

51 FDA, *Summary of Labeling Requirements*, available at http://www.fda.gov/Cosmetics/Labeling/Regulations/ucm126438.htm.

52 7 U.S.C. §§ 136-136y.

53 21 U.S.C. §§ 301-399d.

54 Pub. L. No. 104-170, 110 Stat. 1489.

55 FIFRA § 2(u), 7 U.S.C. § 136(u). FIFRA also defines the term "active ingredient," in pertinent part, to mean "an ingredient which will prevent, destroy, repel, or mitigate any pest." FIFRA § 2(a)(1), 7 U.S.C. § 136(a)(1).

56 40 C.F.R. § 152.15.

57 FIFRA § 2(t), 7 U.S.C. § 136(t); *see also* 40 C.F.R. § 152.5.

58 40 C.F.R. § 158.2100(b).

59 40 C.F.R. § 174.3.

60 40 C.F.R. § 152.15(a)-(c). EPA's regulations provide exemptions from FIFRA regulation. These include the following: certain substances or articles are not intended for use against "pests" and thus are not pesticides; certain products are not intended to prevent, destroy, mitigate, or repel pests and thus are not pesticides; certain pesticides are regulated by other federal agencies and are exempt from all FIFRA requirements; certain pesticides or classes of pesticides are of a character not requiring FIFRA registration; and certain otherwise regulated pesticides may be transferred, sold, or distributed without registration.

61 FIFRA § 2(bb), 7 U.S.C. § 136(bb).

62 40 C.F.R. § 172.48.

63 40 C.F.R. § 172.50.

64 iGEM, *iGEM Competition*, available at http://igem.org/Main_Page.

65 National Chiao Tung University's iGEM Team, available at http://2014.igem.org/Team:NCTU_Formosa.

66 Wikipedia, *Pheromone biosynthesis activating neuropeptide*, available at http://en.wikipedia.org/wiki/Pheromone_biosynthesis_activating_neuropeptide.

67 40 C.F.R. § 152.25(b). A pheromone trap is "a device containing a pheromone or an identical or substantially similar compound used for the sole purpose of attracting, and trapping or killing, target arthropods. Pheromone traps are intended to achieve pest control by removal of target organisms from their natural environment and do not result in increased levels of pheromones or identical or substantially similar compounds over a significant fraction of the treated area." 40 C.F.R. § 152.25(b)(4).

68 40 C.F.R. § 152.25(b)(2).

69 15 U.S.C. §§ 2601-2695d.

70 EPA, *Pesticide Registration Manual: Chapter 3 -- Additional Considerations for Biopesticide Products*, available at http://www2.epa.gov/pesticide-registration/pesticide-registration-manual-chapter-3-additional-considerations#pheromone.

71 TSCA §§ 5(a)(1) and 8(f), 15 U.S.C. §§ 2601(a)(1) and 2607(f).

72 *See* for example TSCA Sections 5(h)(1) and (4), and associated regulations.

73 40 C.F.R. §§ 704.3, 716.3, 717.3(e), 720.3(r).

74 TSCA § 3(2)(A), 15 U.S.C. § 2602(A).

75 Commercial chemical substances produced by microorganisms are also separately subject to new chemical requirements if the substances are not otherwise listed on the TSCA Inventory of chemical substances.

76 This absence is a bit conspicuous given the Asilomar Conference was convened in 1975, a year before Congress enacted TSCA. Senator John V. Tunney, a California Democrat, introduced the Senate bill that eventually was enacted. Given the interest in the Asilomar Conference, it seems a little odd to conclude that genetically engineered organisms are plainly within TSCA's scope despite Congress's complete silence on the subject.

77 Louis S. Sorell, Biotechnology Regulation Under the Toxic Substances Control Act, 3 *Pace Envtl. Rev.* 57(2985) at 66. Note also that as a matter of policy, EPA, in its proposed TSCA biotechnology rule (59 Fed. Reg. 45527 (Sept. 1, 1994)), limited the rulemaking to microorganisms while stating that "plants and animals could also be chemical substances under TSCA."

78 40 C.F.R. § 725.3.

79 40 C.F.R. § 725.1(a), 725.3.

80 40 C.F.R. § 725.3.

81 40 C.F.R. § 725.8(b)

82 G. Mandel and G. Marchant, Evolving Technology Regulation: Governance at a Temporal Distance, included in Bridging Distances in Technology and Regulation, edited by R. Leenes & E. Kosta (2013).

83 With the advent of synthetic biology, EPA's distinction between intergeneric and non-intergeneric microorganisms actually runs afoul of the dictate of the Coordinated Framework that the products of biotechnology should be regulated based on the product itself, not based on the process by which it was made (Office of Science and Technology Policy 1986). EPA's current regulations would differentiate between intergeneric microorganism produced by traditional genetic modification techniques (which would be subject to the regulations) and the identical microorganism which is produced *de novo* using synthetic biology techniques (potentially not subject to the regulations because it did not involve an "intergeneric" transfer).

84 EPA, *Microbial Products of Biotechnology Summary of Regulations under the Toxic Substances Control Act,* available at http://www.epa.gov/biotech_rule/pubs/fs-001.htm.

85 40 C.F.R. § 725.67(a), (b). Exemptions from notification requirements include: (1) the R&D exemption; (2) the Tier I or Tier II exemption; and (3) the Test Market Exemption (TME). If the company can satisfy the criteria for any of these exemptions, it may, depending on the particular exemption, commence manufacture or importation without notifying EPA (in the case of R&D activities conducted "inside a structure," as discussed further below) or may obtain expedited EPA review (*i.e.*, a 45-day review for a TME rather than a 90-day MCAN review).

86 62 Fed. Reg. 17909, 17923. (Apr. 11, 1997).

87 40 C.F.R. §§ 725.234(d), 725.3. EPA further provides the following regarding the containment and/or inactivation controls: "(1) Selection and use of containment and/or inactivation controls inside a structure for a particular microorganism shall take into account the following: (i) Factors relevant to the organism's ability to survive in the environment. (ii) Potential routes of release in air, solids and liquids; in or on waste materials and equipment; in or on people, including maintenance and custodial personnel; and in or on other organisms, such as insects and rodents. (iii) Procedures for transfer of materials between facilities. (2) The technically qualified individual's selection of containment and/or inactivation controls shall be approved and certified by an authorized official (other than the TQI) of the institution that is conducting the test prior to the commencement of the test. (3) Records shall be developed and maintained describing the selection and use of containment and/or inactivation controls, as specified in Section 725.235(c). These records, which must be maintained at the location where the research and development activity is being conducted, shall be submitted to EPA upon written request and within the time frame specified in EPA's request. (4) Subsequent to EPA review of records in accordance with paragraph (d)(3) of this section, changes to the containment/inactivation controls selected under paragraph (d)(1) of this section must be made upon EPA order. Failure to comply with EPA's order shall result in automatic loss of eligibility for an exemption under this section." 40 C.F.R. § 725.234(d).

88 40 C.F.R. §§ 725.205, 725.234(a).

89 40 C.F.R. § 725.234(c).

90 40 C.F.R. § 725.234(b).

91 40 C.F.R. § 725.3.

92 40 C.F.R. § 725.234(e). EPA's regulations set forth when notification procedures are required, and if so, the procedure in which such notifications must be made. *See* 40 C.F.R. § 725.235(a), (b).

93 40 C.F.R. § 725.255.

94 40 C.F.R. §§ 725.260, 725.3.

95 40 C.F.R. § 725.260.

96 40 C.F.R. § 725.270(b).

97 *Id.*

98 40 C.F.R. Part 725, Subpart D.

99 40 C.F.R. § 725.424. EPA is considering adding certain strains of two additional microorganisms to this general exemption (77 Fed. Reg. 54499 (Sept. 5, 2012)).

100 40 C.F.R. § 725.428.

101 40 C.F.R. § 725.450(b).

102 40 C.F.R. § 725.470(e).

103 40 C.F.R. §§ 725.300, 725.305.

104 EPA, "Points to Consider in the Preparation of TSCA Biotechnology Submissions for Microorganisms" (Points to Consider) (June 2, 1997) at 13, available at http://www.epa.gov/biotech_rule/pubs/pdf/ptcbio.pdf.

105 40 C.F.R. § 725.370.

106 40 C.F.R. § 725.370.

107 7 U.S.C. § 7701 *et seq*.

108 *Center for Food Safety v. Vilsack*, 718 F.3d 829, 834 (9th Cir. 2013).

109 7 U.S.C. § 7702(14).

The PPA defines "plant" as "any plant (including any plant part) for or capable of propagation, including a tree, a tissue culture, a plantlet culture, pollen, a shrub, a vine, a cutting, a graft, a scion, a bud, a bulb, a root, and a seed." 7 U.S.C. § 7702(13). It defines "plant product" as "(A) any flower, fruit, vegetable, root, bulb, seed, or other plant part that is not included in the definition of plant; or (B) any manufactured or processed plant or plant part." 7 U.S.C. § 7702(15).

110 Part 340 is entitled "Introduction of Organisms and Products Altered or Produced Through Genetic Engineering Which Are Plant Pests or Which There Is Reason to Believe Are Plant Pests."

111 7 C.F.R. § 340.1. This regulatory definition closely tracks the definition of "plant pest" in the PPA, at 7 U.S.C. § 7702(14).

112 7 C.F.R. § 340.1. The corresponding "groups of organisms which are or contain plant pests" are listed at length in Section 340.2(a), subject to the exemptions identified in Section 340.2(b).

113 A note to Section 340.0 states that "the introduction of organisms and products altered or produced through genetic engineering that are plant pests or are believed to be plant pests" are within the coverage of Part 340. 7 C.F.R. § 340.0 n. 1.

114 Notification is characterized as applying typically to low-risk plants, but a critic of APHIS's implementation of the PPA cites widespread use of this pathway and points to what she views as pervasive deficiencies in the process. *See* E. Montgomery, *Genetically Modified Plants and Regulatory Loopholes and Weaknesses Under the Plant Protection Act*, 37 Vt. L. Rev 351, 366-367 (2012-2013) (Montgomery).

115 *See* 7 C.F.R. § 340.4, addressing "permits for the introduction of a regulated article."

116 7 C.F.R. § 340.6.

117 *See Center for Food Safety v. Vilsack,* 718 F.3d at 835. The data APHIS reviews include, but are not limited to, the field test results.

118 7 C.F.R. § 340.6.

119 42 U.S.C. § 4321 *et seq.*

120 Venter Report at 25.

121 7 U.S.C. § 7712(f).

122 *See Center for Food Safety v. Vilsack*, 718 F.3d at 836 and 843.

123 7 C.F.R. § 360.100.

124 7 C.F.R. § 360.300.

125 718 F.3d 829, *supra*, note 108.

126 The related litigation includes the lawsuit that culminated in the Supreme Court's decision in *Monsanto Co. v. Geertson Seed Farms*, 561 U.S. 139 (2010). The lawsuit sought to require APHIS to prepare an EIS in connection with the deregulation of RRA. The Ninth Circuit noted that the Supreme Court decision was directed only to the scope of the injunction issued by a district court pending preparation of the EIS by APHIS and therefore did not affect the issues for decision in *Center for Food Safety v. Vilsack*, 718 F.3d at 837-838.

127 In so doing, the Ninth Circuit affirmed a district court ruling upholding the deregulation decision. *See Center for Food Safety v. Vilsack*, 844 F. Supp. 2d 1006 (N.D. Cal. 2012).

128 718 F.3d at 836-837.

129 *Id.* at 841.

130 *Id*.

131 *Id*. at 843.

132 Perceived deficiencies in the PPA as a tool for regulating genetically modified plants and crops are doubtless magnified by a recent judicial ruling that the PPA expressly preempts state or local laws prohibiting the cultivation of genetically modified plants to the extent that those plants are regulated under federal law and 7 C.F.R. Part 340. *Hawaii Floriculture & Nursery Ass'n v. County of Hawaii,* No. 14-cv-00267 (D. Hawaii) (Nov. 26, 2014). As a result, the district court issued an injunction against the implementation of Hawaii County Ordinance 13-121.

133 *See, e.g*., Montgomery at 366-369.

134 *See id.* at 369-370.

135 *See* Venter Report at 25-27.

136 Reportedly, other companies are using genome-editing techniques to sell herbicide-resistant canola. *See infra*, note 140.

137 BioGlow, available at http://www.bioglow-tech.com/.

138 Glowing Plant, available at http://www.glowingplant.com/.

139 Kickstarter, *Glowing Plants: Nautral Lighting with no Electricity*, available at https://www.kickstarter.com/projects/antonyevans/glowing-plants-natural-lighting-with-no-electricit.

140 Andrew Pollack, *By "Editing" Plant Genes, Companies Avoid Regulation*, N.Y. Times, Jan. 1, 2015, accessed at http://www.nytimes.com/2015/01/02/business/energy-environment/a-gray-area-in-regulation-of-genetically-modified-crops.html?_r=0.

141 Letter from Richard Shank, Ph.D., Senior Vice President Regulatory and Government Affairs, The Scotts Miracle-Gro Company, to Tom Vilsack, Secretary, U.S. Department of Agriculture (USDA), September 13, 2010, available at http://www.aphis.usda.gov/brs/aphisdocs/scotts_kbg.pdf (response to Dr. Richard Shank, The Scotts Miracle-Gro Company, from Michael C. Gregoire, Deputy Administrator, USDA APHIS, July 1, 2011, available at http://www.aphis.usda.gov/brs/aphisdocs/scotts_kbg_resp.pdf).

142 Letter from Richard Shank, Ph.D., Senior Vice President Regulatory and Governmental Affairs, The Scotts Miracle-Gro Company, to Michael C. Gregoire, Deputy Administrator, Biotechnology Regulatory Services, April 5, 2013, available at http://www.aphis.usda.

gov/biotechnology/downloads/reg_loi/scotts_tall_fescue_air_cbidel_20130903.pdf.

143 Letter from Michael C. Gregoire, USDA APHIS, to Dr. Alexander Krichevsky, BioGlow LLC, March 21, 2013, available at http://www.aphis.usda.gov/biotechnology/downloads/reg_loi/aphis_response_bioglow_032113.pdf.

144 Letter from Michael Firko, Ph.D., Deputy Administrator, Biotechnology Regulatory Services, to Mr. Antony Evans, Glowing Plant, Inc., December 23, 2014, available at https://www.dropbox.com/s/h8aujio5whb1nfw/Aphis%20am%20l%20regulated%20response.rotated.pdf?dl=0, linked from http://blog.glowingplant.com/.

145 *Id*.

146 APHIS, *Biotechnology Regulatory Services, Factsheet* (Feb. 2015), available at http://www.aphis.usda.gov/publications/biotechnology/2015/faq_withdrawal.pdf.

147 Importation, Interstate Movement, and Release Into the Environment of Certain Genetically Engineered Organisms, 80 Fed. Reg. 11598 (Mar. 4, 2015), available at http://www.aphis.usda.gov/brs/fedregister/brs_20150304.pdf.

148 *Id*.

149 42 U.S.C. § 4321 *et seq*.

150 *Department of Transp. v. Public Citizen*, 541 U.S. 752, 756 (2004) (*quoting* 42 U.S.C. § 4321).

151 NEPA § 102(2)(C), 42 U.S.C. § 4332(2)(C). Federal actions are considered to include funding for projects not directly initiated by a federal agency.

152 42 U.S.C. § 4332(2).

153 *NRDC v. FAA*, 564 F.3d 549, 556 (2d Cir. 2009) (internal quotation marks omitted).

154 *Department of Transp. v. Public Citizen*, 541 U.S. at 756-57. The corollary is that a court's only role in reviewing agency action for compliance with the NEPA "is to insure that the agency has taken a hard look at environmental consequences." *Coalition on West Valley Nuclear Wastes v. Chu*, 592 F.3d 306, 310 (2d Cir. 2009) (internal quotation marks omitted). "Significantly, 'if the adverse environmental effects of the proposed action are adequately identified and evaluated, the agency is not constrained by NEPA from deciding that other values outweigh the environmental costs.'" *NRDC v. FAA*, 564 F.3d at 556, *quoting Robertson v. Methow Valley Citizens Council,* 490 U.S. 332, 350 (1989).

155 40 C.F.R. §§ 1500-15081.

156 40 C.F.R. §§ 1507.3(b)(2), 1508.4.

157 40 C.F.R. §§ 1508.9(a), 1508.13. If it becomes apparent that an EIS will be required, the agency may proceed directly to that stage without undertaking the exercise of an EA.

158 7 C.F.R. § 372.5(c)(3)(ii).

159 Notification and field testing under APHIS regulations are discussed above.

160 718 F.3d 829, *supra*, note 108.

161 561 U.S. 139, *supra*, note 126.

162 *Geertson Seed Farms v. Johanns*, No. C06–01075, 2007 WL 518624, at *10–12 (N.D.Cal. Feb. 13, 2007) (unpublished decision).

163 *Geertson Seed Farms v. Johanns,* 570 F.3d 1130, 1133-34 (9th Cir. 2009), *cert. granted sub nom. Monsanto Co. v. Geertson Seed Farms*, 130 S. Ct. 1133 (2010).

164 The four necessary factors are irreparable harm, inadequacy of legal remedies, a balance of hardships favoring the moving party, and the absence of injury to the public interest if an injunction is issued.

165 The Court elaborated as follows on the flaws in the district court's approach: ". .

.[T]he terms of the District Court's injunction do not just enjoin the *particular* partial deregulation embodied in APHIS's proposed judgment. Instead, the District Court barred the agency from pursuing *any* deregulation -- no matter how limited the geographic area in which planting of RRA would be allowed, how great the isolation distances mandated between RRA fields and fields for growing non-genetically-engineered alfalfa, how stringent the regulations governing harvesting and distribution, how robust the enforcement mechanisms available at the time of the decision, and -- consequently -- no matter how small the risk that the planting authorized under such conditions would adversely affect the environment in general and respondents in particular." 561 U.S. at 161.

166 *See* the discussion of *Center for Food Safety v. Vilsack*, above. As summarized by the court, "[t]he 2011 ROD [Record of Decision] noted that although RRA was created using a plant pest (the Agrobacterium), the genetically modified plant did not present any direct or indirect plant pest risks and therefore should be granted 'nonregulated status.' The ROD stated that because RRA will not damage or injure other plants, it does not present a greater plant pest risk than conventional alfalfa." 718 F.3d at 838.

167 *Center for Food Safety v. Vilsack*, 636 F.3d 1166 (9th Cir. 2011).

168 *Id*. at 1173.

169 *Id.*

170 40 C.F.R. § 1508.9; 21 C.F.R. § 25.40(a).

171 21 C.F.R. § 25.22(b).

172 Consistent with CEQA's regulations, under 40 C.F.R. § 25.21, in extraordinary circumstances an EA (at a minimum) will be required for actions that otherwise would be categorically excluded:

As required under 40 CFR 1508.4, FDA will require at least an EA for any specific action that ordinarily would be excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment (see 40 CFR 1508.27 for examples of significant impacts). Examples of such extraordinary circumstances include:

Actions for which available data establish that, at the expected level of exposure, there is the potential for serious harm to the environment; and

(b) Actions that adversely affect a species or the critical habitat of a species determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Flora and Fauna to be endangered or threatened or wild flora or fauna that are entitled to special protection under some other Federal law.

173 40 C.F.R. § 25.40(b).

174 40 C.F.R. § 25.20(l) and (m), respectively.

175 40 C.F.R. § 25.20(i).

176 FDA, *Statement of Policy -- Foods Derived from New Plant Varieties*, 57 Fed. Reg. 22984 (May 29, 1992), *available at* http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Biotechnology/ucm096095.htm (discussed in a Library of Congress report, "Restrictions on Genetically Modified Products: United States," available at http://www.loc.gov/law/help/restrictions-on-gmos/usa.php).

177 21 U.S.C. § 360b(a).

178 21 C.F.R. § 514.1(b)(14).

179 FDA, *Guidance for Industry: Regulation of Genetically Engineered Animals Containing Heritable rDNA Constructs* (June 2015) (GE Guidance) at 20, available at http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf.

180 *Id* at 12.

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