Commentary

Industrial Biotechnology: Coordinated Framework Make-Over and Lots More

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The summer of 2015 was surprisingly busy in the industrial biotechnology policy and regulatory arenas with three important announcements generating lots of buzz. On July 2, 2015, the White House Office of Science and Technology Policy (OSTP), the Office of Management and Budget (OMB), the US Trade Representative, and the Council on Environmental Quality issued a memorandum directing the US Environmental Protection Agency (EPA), the US Food and Drug Administration (FDA), and the US Department of Agriculture (USDA) to update and modernize the Coordinated Framework for the Regulation of Biotechnology (Coordinated Framework). A few weeks later, EPA's Office of Pollution Prevention and Toxics (OPPT) announced a project intended to support public dialog concerning the development and use of biotechnology by developing a new algae ''how to'' document for Toxic Substances Control Act (TSCA) purposes, and to help jump start much needed public discourse around the topic of biotechnology in general. Finally, OPPT also announced that it is updating its *Points to Consider in the Preparation of TSCA Biotechnology Submissions for Microorganisms* (Points to Consider). Each of these developments is important. This article discusses these initiatives, offers insights on why stakeholders should applaud these opportunities, and urges stakeholders to seize the moment and to engage vigorously in them. Engagement will ensure that the government and other interested parties, including the public, are fully informed about these emerging technologies and their importance to society, and are confident in the government's oversight of them.

Coordinated Framework for Regulation of Biotechnology

Federal oversight of products of biotechnology is directed through the Coordinated Framework issued in 1986 by the Reagan Administration's White House OSTP, and updated in 1992.[1] The core premise of the Coordinated Framework is that the legal authorities that existed in 1986, statutory authorities that remain largely unchanged today, provide federal regulators sufficient authority to manage any health and/or environmental risk that products of biotechnology may pose. Recognizing that many federal agencies have jurisdiction over products of biotechnology, the Coordinated Framework sets forth an organizational blueprint for federal agency oversight and establishes lead responsibilities for the federal oversight of products of biotechnology. The Coordinated Framework was intended to be a flexible governance construct capable of nimbly adjusting to new science and innovation, and not shackle the oversight of new products to inflexible regulatory templates. Risks are assessed on a case-by-case, product-by-product basis, and federal oversight focuses on a product's application and its intended use, not on the technology itself.

Under the Coordinated Framework, three federal agencies are principally responsible for regulating products of biotechnology: USDA, and in particular its Animal and Plant Health Inspection Service (APHIS), EPA, and FDA. APHIS is responsible for regulating field trials of genetically modified crops and plants under the Plant Protection Act (PPA). EPA regulates genetically engineered microbes under TSCA, and genetically engineered pesticides and pesticides incorporated into plants under the Federal Insecticide, Fungicide, and Rodenticide Act (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.

Federal Food, Drug, and Cosmetic Act (FFDCA)

FDA's oversight under the FFDCA is extensive. 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. 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.[2] Any regulatory approach driven by statutorily defined ''products'' necessarily makes it less than nimble in the context of fast changing innovations in the area of industrial biotechnology. Both the inflexibly defined products and the separate FDA ''Centers'' that regulate them contribute to a balkanization of the review process. The inevitable, compartmentalizing 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 the diversity and complexity of today's products of industrial biotechnology emerged.

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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 regulatory infrastructure built around it challenge the efficient and comprehensive review of products of all new technologies, including biotechnology.

A detailed overview of FDA's authority to evaluate products of biotechnology is beyond this article's scope. An excellent summary of FDA's regulatory authority is found in the 2014 report prepared by the J. Craig Venter Institute.[3] As noted in the Venter 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.[4]

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 ensure 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.[5,6] 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 change to the manufacturing process 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 document 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.''[6]

Federal Insecticide, Fungicide, and Rodenticide Act

FIFRA is also heavily reliant on 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: 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; 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 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.[7]

Under FIFRA, new pesticides must be registered with EPA before they can be commercially marketed. To register a pesticide under FIFRA, EPA must determine, among other issues, that the pesticide product when used as intended ''will not generally cause unreasonable adverse effects on the environment.'' FIFRA defines the term ''unreasonable adverse effects on the environment'' to mean any unreasonable risk to man or the environment, taking into consideration the costs and benefits of any pesticide, or dietary risk from pesticide residues.[8] Benefits are to be taken into account in making the safety determination under FIFRA, but if a food use tolerance is required for a particular product registration, EPA must also find with ''reasonable certainty'' that ''no harm will result from aggregate exposure to the pesticide residue.''

Under FIFRA, the statutory definition of pesticide turns on the intent of the manufacturer to produce a pesticide, not on the manufacturing process itself. Accordingly, EPA has interpreted its regulatory authority to include plants that have been genetically modified through recombinant DNA (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's regulatory program for 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 meet 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.[9] 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.[10] The review process is relatively short, as EPA intended the BNP to apply to smaller field test plots of less than 1 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 in 1991 for two *Pseudomonas* fluorescent strains that were genetically engineered to express two types of delta endotoxin genes from *Bacillus thuringiensis* (Bt) for insect control. The registration process for this product began at least 5 years earlier when the registrant began working with EPA on small scale field testing.

Toxic Substances Control Act

TSCA is the federal law that regulates ''chemical substances.'' Excluded from TSCA and its implementing regulations are chemicals that are regulated under other statutes, including food,

drugs, cosmetics, and pesticides. Congress enacted TSCA in 1976 and intended it to serve as a gap-filler: if a chemical substance is not regulated under another statutory program, it is subject to TSCA.TSCA has not been substantively amended with respect to chemical management since its enactment almost 40 years ago, but vigorous efforts to modernize TSCA are underway in Congress with the hope that legislation will be enacted later in 2015.

The Coordinated Framework provides that the US government consider microorganisms and their DNA and rDNA molecules as ''chemical substances'' as defined under and thus subject to TSCA.[11] (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.) Chemical substance is broadly defined, and at their basic level, DNA molecules are chemical substances of ''a particular molecular identity.''

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.''[12] An ''intergeneric microorganism'' is a microorganism formed by the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera.[13] This classification 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.''[14] EPA states that ''[m]icroorganisms that are not intergeneric are automatically included on the Inventory,'' because conceptually they are existing chemical substances.[15]

EPA's implementing regulations require manufacturers of new intergeneric microorganisms for commercial purposes to submit a notification to EPA or otherwise to 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.[16] 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 research and development (R&D) or for commercial use, and whether the activity is conducted in an enclosed structure or involves environmental release. TSCA and EPA 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.''[17]

In the preamble to the final microorganism regulations, EPA expressed its concern with R&D activities with microorganisms because EPA believes that living microorganisms may ''reproduce and increase beyond the number initially introduced, may establish in the environment, and may spread beyond the test site.''[18] 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.''[19] 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, there must not be any ''intentional testing of a microorganism outside of a structure,'' the microorganism must be used by, or directly under the supervision of, a technically qualified individual, as defined in EPA's regulations, 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.[20–24]

For R&D activities that do not qualify for the contained structure exemption, EPA requires the submission of a TSCA Experimental Release Application (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.[25] 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.[26] The submitter must provide this information to the extent it is ''known to or reasonably ascertainable by the submitter.''[27] 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.[28] If 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.[29]

For commercial activities, EPA has implemented premanufacture notification (PMN) and exemption procedures. The notification is referred to as a Microbial Commercial Activity Notice (MCAN).[30] EPA specifies in its MCAN regulations the information that the notice 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 Significant New Use Rule (SNUR), which would require future notifications to EPA concerning ''significant new uses'' of the microorganism.

EPA has established a two-tiered exemption from notification requirement for commercialization of microorganisms that meet specified criteria. To qualify for the Tier I exemption: the microorganism must be one of 10 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 must submit a certification at least 10 days prior to commencing initial manufacture or import of the new microorganism; and the manufacturer or importer must comply with recordkeeping requirements.[31] The Tier II exemption provides for an expedited review of microorganisms that satisfy Tier I requirements, except that the facility must also meet all necessary requirements for physical containment and control technologies.[32] 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.[33] EPA will approve or deny the Tier II exemption request no later than 45 days after EPA receives the request.[34]

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).[35] 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.''[36] EPA will either approve or deny a TME application no later than 45 days after receipt, and may impose restrictions with approval.[37] The submitter ''may only proceed with test marketing activities after receipt of EPA approval.''[38]

Plant Protection Act (PPA)

APHIS is tasked with regulating field trials of genetically modified crops and plants under the PPA, enacted in 2000.[39] 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.'''[40] When the Coordinated Framework 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; and (H) Any article similar to or allied with any of the articles specified in the preceding subparagraphs.''[41]

The APHIS implementing regulations at 7 C.F.R. Part 340 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.''[42,43]

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 ''[a]ny 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.''[44]

This definition of a ''regulated article'' incorporates a 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 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 generically modified organisms that otherwise satisfy the general definition of a plant pest. As a practical matter, most genetically modified organisms that could be deemed to be a potential plant pest are genetically modified plants.

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.[45] The second, more elaborate pathway is a field testing program under 7 C.F.R. § 340.4 that requires 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.[46] 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. A permit will be issued only if

APHIS decides that the testing can go forward, subject to any necessary conditions, without posing plant pest-associated risks beyond the test site. Should a field test yield favorable results, a person may petition APHIS for a ''determination of nonregulated status.''[47] Also referred to as ''deregulation,'' this is the third option and clears a path for seeking commercialization. The contents of this data-driven, substantive filing and the procedures for evaluating it are specified in the regulations.

With nearly three decades of field test permissions 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 had been deregulated as of August 2013.[48]

The OSTP Memorandum

The foregoing, exceedingly cursory overview sets the stage for a discussion on the OSTP memorandum issued on July 2, 2015, which directs EPA, FDA, and USDA to initiate a process to update and modernize the Coordinated Framework. A July 2, 2015, OSTP blog item titled ''Improving Transparency and Ensuring Continued Safety in Biotechnology'' notes that the complexity of the array of regulations described above 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.'' This understated observation holds the key to the critical need for the ''modernization'' exercise. 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.'' Given the bewildering complexity of the regulatory process under each statute for biotechnology product approval, achieving these stated objectives will not be easy. That said, achieving these objectives is essential.

The OSTP 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 intended to 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 both potential new risks and frameworks for risk assessment, and areas in which the risks or lack of risks relating to the products of biotechnology are well understood. The review will help inform future policy making. Due to the rapid pace of change in this arena, an external analysis should be completed at least every 5 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 memorandum in agency fiscal year (FY) 2017 budget requests and, as appropriate, in future budget submissions
- **Annual Reporting:** For at least 5 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. The Executive Office of the President will make this report available to the public

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 is to occur in Washington, DC, in fall 2015. According to the blog item, the update to the Coordinated Framework will undergo public notice and comment before it is issued in final.

EPA Biotechnology Initiatives

EPA's August announcement that it is developing a project intended to support public dialog concerning the development and use of biotechnology aligns well with the goals of the OSTP mandate, and has broad implications. As noted above, EPA has oversight responsibility for the production and use of intergeneric microorganisms, including cyanobacteria, eukaryotic microalgae, and their products by application of genetic engineering approaches. OPPT's August-posted document states that it is focusing its project around biotechnology algae applications.

As part of its efforts to implement TSCA, EPA provides technical support for reporting on new chemical substances and microorganisms that are not yet in commerce. EPA's 1997 Points to Consider document assists those who intend to submit TSCA MCANs or TERAs for various commercial products. The Points to Consider document helps submitters identify and organize the information and data they provide to inform EPA's required risk assessments. An important component of EPA's recent announcement is that it is ''currently updating the Points to Consider to accommodate the development of new information relevant to risk assessment of biotechnology products regulated under TSCA.'' According to EPA, the Points to Consider document does not currently provide specific support for those using the emerging technologies of biotechnology algae production. EPA states that to keep its risk assessment process for biotechnology algae open and transparent, it intends to develop a ''separate document on the scientific and technological issues it currently understands to be key and unique for evaluating risks'' from the production and use of biotechnology algae. EPA will develop its ''Considerations for Biotechnology Algae'' document for biotechnology algae in parallel with updating the Points to Consider document.

According to EPA, the updates to the Points to Consider ''will be enhancements of the current detailed, how-to content for submitters to think about as they prepare submissions.'' EPA notes that the current document is organized to reflect the components of risk assessments for microorganisms, but this format is not optimally designed to address specific considerations informing the evaluation of algal biotechnologies submitted under TSCA. The algae document will evolve as a separate, stand-alone document so that EPA can organize the information in a consolidated manner that can assist those developing new microbial technology applications that have emerged since EPA last revised the Points to Consider.

EPA notes that ''[e]ven those applications that employ both algae and biotechnologies simultaneously can be highlighted in a way that the current *Points to Consider* cannot readily do.'' According to EPA, the separate biotechnology algae document can serve other purposes, unlike the Points to Consider. EPA states that the document ''can also – through its use as an example of an actual, practical governance tool – help advance discourse around broader societal implications of biotechnology. Once fully developed, it will be a source of information that could be folded into the *Points to Consider*, within its current structure or in other ways, such as an addendum, or it could remain as a stand-alone complement to the *Points to Consider*.''

EPA states that it expects that the process of revising the Points to Consider and developing a companion document on considerations for biotechnology algae will lead to the identification of technical, environmental, and social science research needs related to the introduction of such products into society. Addressing these research needs may directly or indirectly support its evaluation of such products under TSCA, as well as more broadly help advance the responsible development and application of biotechnology. Therefore, as EPA develops its considerations document for biotechnology algae, EPA states that it ''welcomes public input not only on technical environmental assessment issues, but also on the societal benefits and implications'' of these products.

EPA intends to facilitate such engagement and scheduled an expert workshop open to the public on September 30, 2015.[49] While the workshop focused on the technical questions that EPA believes are important to its development of a biotechnology algae considerations document, EPA provided an opportunity to stakeholders and the general public to comment on any aspects of biotechnology algae they believe are relevant to EPA's mission.

Following the workshop, EPA is considering the public input as it begins to draft its biotechnology algae considerations document. EPA expects that feedback on the biotechnology algae document will also inform its update of the Points to Consider document. EPA recognizes that some input may relate to issues that fall outside the scope of the document and EPA's premanufacture review authority under TSCA. EPA expects that public awareness of its biotechnology algae document will lead to broader questions about the introduction of genetically modified organisms and other biotechnology products into society.

A key driver for OPPT's interest in developing both documents is the increase in the number of TSCA biotechnology submissions. As of June 2015, the number of submissions had already surpassed previous years' totals (*Fig. 1*). According to EPA, newer submissions mostly employ some form of biotechnology, such as the use of chemically synthesized, codon optimized genes. Importantly, EPA notes that some of the algae submissions are from companies that ''have had little or no experience with new substance review under TSCA.'' EPA expects that for these companies in particular, it will be useful to have guidance on how to submit an MCAN or TERA that includes information to help answer the questions that EPA will ask in its evaluation of their submissions. Consolidating information on emerging technologies will make it easier for interested parties to understand both what information is needed to support risk assessments and why such information is needed.

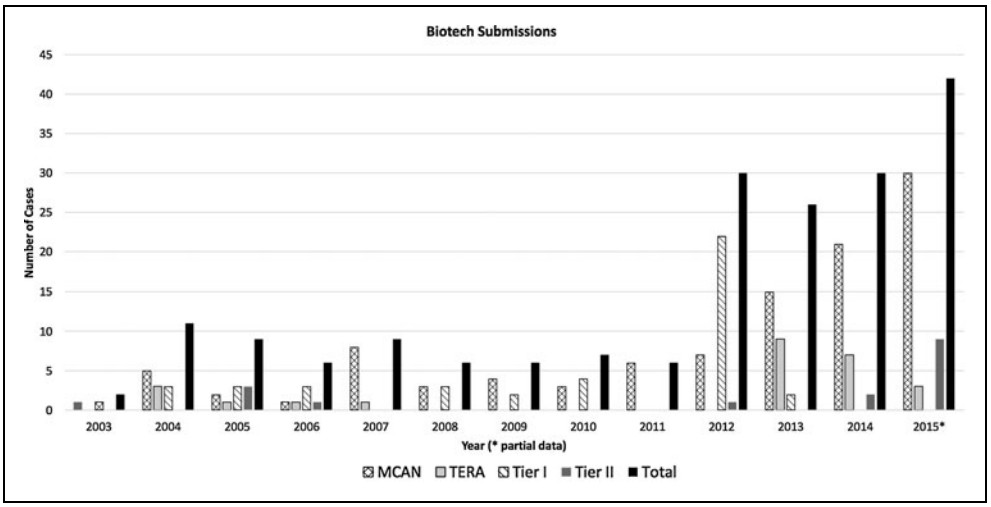

Fig. 1. Increases in TSCA biotech cases, 2003-current. Source: Environmental Protection Agency (Available at www.epa.gov).

EPA states that it recognizes the potential of biotechnology to create new benefits for society, and, therefore, supports its development in the US. According to EPA, the biotechnology algae considerations document ''will increase the likelihood that MCAN and TERA submitters receive expeditious EPA review of their submissions, and that any products that are approved, and ultimately commercialized, maximize their benefits to society by minimizing their potential for negative impacts on human health and the environment.'' EPA concludes its notice with observing that as with other emerging technologies, it ''believes that the responsible development of biotechnology should include discourse around introducing biotechnology applications and products into society.'' EPA's creation of a biotechnology algae considerations document can play a positive role in advancing public discourse and supporting the responsible development of biotechnology products.''

Discussion

OSTP's mandate to modernize the Coordinated Framework and OPPT's biotechnology projects herald much needed work and the opportunity for public engagement in biotechnology, both of which are absolutely essential and overdue. That products of biotechnology are critically important to solving some of the world's most vexing problems is indisputable, as is the simple fact that these products are evolving at a pace and with a complexity that, without change, could outstrip the limited (and shrinking) capacities of the federal government comfortably or efficiently to review them and ensure their safety. A number of recent reports have convincingly outlined the reasons why the Coordinated Framework can no longer nimbly, clearly, or comprehensively regulate products of biotechnology and call for exactly what OSTP announced this summer. As noted, the Venter report's landmark analysis of the domestic biotechnology regulatory system highlighted the critical need for modernizing the Coordinated Framework. More recently, the National Research Council of the National Academies issued, on March 13, 2015, *Industrialization of Biology*: *A Roadmap to Accelerate the Advance Manufacturing of Chemicals*. The report, prepared by the Board on Chemical Sciences and Technology, Board on Life Sciences, Division on Earth and Life Studies, identified the challenges and opportunities posed by the current regulatory system relating to biotechnology and synthetic biology.[50]

Apart from all the relatively obvious capacity issues that daily challenge the federal agencies whose job it is to ''coordinate'' under the Coordinated Framework–staffing, technical literacy, and funding, to name a few–the novelty and complexity of biotechnology innovations today strain the jurisdictional boundaries set out under the statutory and governance frameworks described briefly above. As an example, consider the jurisdictional confusion around certain pest control technologies. Genetically engineered insects being developed for plant pest control are considered under the oversight of USDA's APHIS, whereas previously approved FDA anti-malaria drugs manufactured using synthetic biology technologies were addressed by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research at FDA. Technologies that control animal populations by sterilization, however, have been regulated by FDA's Center for Veterinary Medicine (CVM). In one recent case, a genetically engineered mosquito strain developed by Oxitec, Ltd. by injecting rDNA into *A. aegypti* eggs, designed to kill the subsequent offspring of mosquitoes, was subject to CVM review as an animal drug.[51] It was determined, after considerable consultation, that CVM's precedent of regulating as animal drugs other animal sterilants used for animal population control was a suitable regulatory pathway for Oxitec's mosquito. This approach was not intuitively obvious to the regulators tasked with providing a regulatory approval pathway for Oxitec's product. The approach was certainly not intuitively obvious to Oxitec before, during, or likely even after the process was finally decided. Some might even argue that EPA should assert jurisdiction under FIFRA as a pest control product. The point here is that a genetically engineered mosquito strain is determined ultimately to be subject to FDA regulation, after considerable uncertainty, debate, and agency deliberation, as an animal drug is evidence of an oversight system that is anything but predictable, transparent, efficient, and user friendly, particularly to the uninitiated or first-time innovator seeking government product approval.

The vagaries of the regulatory gauntlet, and the delays and business disruptions they occasion, are experienced disproportionally by business entities least able to address them but most essential to innovation itself, namely the quintessential small-business start-up that develops a breathtakingly innovative product and finds itself shell-shocked in trying to navigate a regulatory pathway in a sometimes incoherent and invariably opaque governance construct. The current system offers little

reason to hope or expect predictability or transparency, and society is the lesser for it. Given the mind-numbing complexity of the jurisdictional maze, 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 innovators to the appropriate agency and office within that agency 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. Yet these are the very questions for which financial backers demand answers often as a predicate for funding.

If the Administration's decision to modernize the Coordinated Framework and OPPT's efforts to provide useful guidance to describe and facilitate the biotechnology approval process help resolve even some of this governance disarray, let's get these initiatives underway as quickly as possible and participate in them robustly. Equally important as the need for clear guidance for the innovator is the urgent need for public engagement. All three initiatives discussed above emphasize the need for and seek public review and engagement in the government's oversight of products of biotechnology. Public discourse is essential to the success of these technologies. If the public is unconvinced that the government is able to review and assure the safety of these technologies, the chance of commercial success is greatly diminished. The Administration's commitment to modernize the Coordinated Framework, and make its application more predictable and transparent will, if implemented as needed, go a long way in ensuring public acceptance of and confidence in these technologies. Collectively, these initiatives will help encourage regulatory transparency and, with robust engagement and careful planning by stakeholders, the public will better appreciate the benefits of biotechnology.

A final thought on the role of TSCA reform legislation. If enacted this year as is hoped by many, the modernizing of the Coordinated Framework may occur on a separate trajectory from TSCA reform implementation, a possibility that poses both risks and opportunities. The tricky part will be ensuring that the modernizing of TSCA and the modernizing of the Coordinated Framework are aligned. If TSCA reform legislation does not advance this year, future legislative efforts may be considered to address some of the more intractable jurisdictional issues that regulatory reform cannot easily resolve.

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3. J. Craig Venter Institute. *Synthetic Biology and the U.S. Biotechnology Regulatory System: Challenges and Options.* (Venter report) May 2014, pgs 18–22. Available at www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-biology-and-the-us-regulatory-system/full-report.pdf (Last accessed August 2015).
4. NEPA § 102(2)(C), 42 U.S.C. § 4332(2)(C): 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.
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7. 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.
8. FIFRA § 2(bb), 7 U.S.C. § 136(bb).
9. 40 C.F.R. § 172.48.
10. 40 C.F.R. § 172.50.
11. TSCA § 3(2)(A), 15 U.S.C. § 2602(A).
12. 40 C.F.R. § 725.3.
13. 40 C.F.R. §§ 725.1(a), 725.3.
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15. 40 C.F.R. § 725.8(b).
16. Mandel G, Marchant G. Evolving technology regulation: Governance at a temporal distance. In: Leenes R, Kosta E (eds). *Bridging Distances in Technology and Regulation* Oisterwijk, The Netherlands: Wolf Legal Publishers, 2013.
17. 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") or may obtain expedited EPA review (i.e., a 45-day review for a TME rather than a 90-day MCAN review).
18. 62 Fed. Reg. 17909, 17923. (Apr. 11, 1997).
19. 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."

20. 40 C.F.R. §§ 725.205, 725.234(a).
21. 40 C.F.R. § 725.234(c).
22. 40 C.F.R. § 725.234(b).
23. 40 C.F.R. § 725.3.
24. 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).
25. 40 C.F.R. § 725.255.
26. 40 C.F.R. §§ 725.260, 725.3.
27. 40 C.F.R. § 725.260.
28. 40 C.F.R. § 725.270(b).
29. 40 C.F.R. § 725.270(b).
30. 40 C.F.R. Part 725, Subpart D.
31. 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]).
32. 40 C.F.R. § 725.428.
33. 40 C.F.R. § 725.450(b).
34. 40 C.F.R. § 725.470(e).
35. 40 C.F.R. §§ 725.300, 725.305.
36. EPA. Points to Consider in the Preparation of TSCA Biotechnology Submissions for Microorganisms. June 2, 1997: pg 13. Available at www.epa.gov/biotech_rule/pubs/pdf/ptcbio.pdf (Last accessed August 2015).
37. 40 C.F.R. § 725.370.
38. 40 C.F.R. § 725.370.
39. 7 U.S.C. § 7701 *et seq*.
40. *Center for Food Safety v. Vilsack*, 718 F.3d 829, 834 (9th Cir. 2013).
41. 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).
42. 7 C.F.R. 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."
43. 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).
44. 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).
45. Montgomery E. *Genetically Modified Plants and Regulatory Loopholes and Weaknesses Under the Plant Protection Act*, 37 Vt. L. Rev 351, 366–367 (2012–2013) (Montgomery). 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.
46. See 7 C.F.R. § 340.4, addressing "permits for the introduction of a regulated article."
47. 7 C.F.R. § 340.6.
48. Venter report, pg 25.
49. 80 Fed. Reg. 51561 (Aug. 25, 2015).
50. National Academy of Sciences. Industrialization of Biology: A Roadmap to Accelerate the Advanced Manufacture of Chemicals. Washington, DC: National Academies Press, 2015. Available at: www.nap.edu/catalog/19001/industrialization-of-biology-a-roadmap-to-accelerate-the-advanced-manufacturing (Last accessed August 2015).
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