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Creative Adaptation: Enhancing Oversight of Synthetic Biology Under the Toxic Substances Control Act

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Synthetic biology is delivering on its promise as an emerging scientific field in providing society with effective new sustainable products in diverse areas including renewable energy, contamination remediation, and medical applications, among others. As is the case with any rapidly evolving technology, the pace of technological innovation challenges regulators' ability to identify and address adequately the substantial uncertainties they confront when discharging their legal obligations under controlling laws to ensure human and environmental safety. This article provides a brief description of synthetic biology, discusses the current domestic regulatory framework that governs the regulation of products of synthetic biology, and focuses narrowly on options and opportunities the US Environmental Protection Agency (EPA), innovators in the area of synthetic biology, and the Toxic Substances Control Act (TSCA)-regulated community at large may wish to consider to enhance TSCA's core adaptive capacity to identify and address potential health and environmental risk implications posed by the commercialization of products of synthetic biology.

Recognizing that comprehensive TSCA legislative reform is still likely years away, stakeholders may be more successful in optimizing TSCA's inherent flexibility as an adaptive governance tool to foster the sustainable commercial development of synthetic biology. The collaborative pursuit of several suggested options now could facilitate the continued thoughtful and prudent development of synthetic biology by increasing public awareness, fostering a better understanding of this important emerging technology, ensuring that the EPA possesses the understanding it needs to discharge its responsibilities, and working to build a stronger collaborative environment among stakeholders and the EPA. Efforts such as these, as well as ensuring adequate EPA resources and capabilities to manage its responsibilities and keep up with evolving technological developments, will do much to ensure public confidence in the safety and commercial benefits of the products of synthetic biology.

Synthetic Biology: A Primer

Synthetic biology is defined succinctly in the recently issued, excellent report prepared by the J. Craig Venter Institute (JCVI), ''Synthetic Biology and the U.S. Biotechnology Regulatory System: Challenges and Options'' as a ''set of techniques that together provide scientists and engineers with far greater capabilities to engineer organisms than previous techniques allowed.''[1] This is not necessarily the best or only definition of this fast emerging field. According to Stanford University's The Kool Group, W. Szybalski, a molecular biologist, coined the term synthetic biology to describe a top-down approach to cellular design. This is in contrast to the chemical approach to cellular design, which is more of a bottom-up strategy, in which nucleic acids, amino acids, and carbohydrates are redesigned and inserted back into living things.[2]

Developments in biology are expected to have a big impact and play an important role in US competitiveness and the bioeconomy. According to some reports, the synthetic biology global market will reach $10.8 billion by 2016.[3] It is no wonder that the Obama Administration renewed its commitment to strengthening and growing bioscience through the issuance of the National Bioeconomy Blueprint in 2012.[4,5] In the Blueprint, the Administration ''outlines steps that agencies will take to drive the bioeconomy—economic activity powered by research and innovation in the biosciences—and details ongoing efforts across the Federal government to realize this goal.'' Synthetic biology is defined in the Blueprint as ''the design and wholesale construction of new biological parts and systems, and the re-design of existing, natural biological systems for tailored purposes, integrates engineering and computer-assisted design approaches with biological research.''[4] The Blueprint outlines five strategic objectives for a bioeconomy with the potential to generate economic growth and address societal needs.

Other definitions of synthetic biology offer variations on a similar theme. The Synthetic Biology Engineering Research Center (synBERC) defines it as ''the design and construction of new biological entities such as enzymes, genetic circuits, and cells or the redesign of existing biological systems…''[6] The Royal

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Academy of Engineering notes, ''Synthetic biology aims to design and engineer biologically based parts, novel devices and systems as well as redesigning existing, natural biological systems.''[7]

Detractors of synthetic biology have offered less flattering definitions of the term. Three self-described ''civil engineering'' groups issued ''The Principles for the Oversight of Synthetic Biology'' in 2012 and described synthetic biology as ''extreme genetic engineering—re-engineering and designing genes and creating entire genomes that do not exist in nature as well as designing and building molecules, cell compounds and organelles to desired specifications.''[8] The coalition calls for a moratorium on the release and commercial use of synthetic organisms until its ''principles necessary for the effective assessment and oversight of'' synthetic biology have been implemented.

The US government has been supportive of this emerging technology, as it has been of other emerging technologies such as nanotechnology. In addition to the 2012 National Bioeconomy Blueprint, Executive Order 13134—Developing and Promoting Biobased Products and Bioenergy—is another expression of the federal government's support for the use of biobased and bioenergy technology to make renewable energy, chemicals, fuel, and related products.[9] It set as a national objective the development of a strategy to stimulate the creation and adoption of technologies needed to make US biobased products globally competitive. The Order states: ''It is the policy of this Administration, therefore, to develop a comprehensive national strategy, including research, development, and private sector incentives, to stimulate the creation and early adoption of technologies needed to make biobased products and bioenergy cost-competitive in large national and international markets.''

The products of synthetic biology are diverse. The Biotechnology Industry Organization (BIO), the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the US and over 30 other nations, lists on its website several current examples of synthetic biology products.[10] According to the website, ''DNA synthesis and DNA sequencing have enabled the construction and rapid characterization of metabolically engineered microorganism strains to produce isoprene. Synthetic biology has enabled the construction of a gene that encodes the same amino acid sequence as the plant enzyme but that is optimized for expression in the engineered microorganism of choice.''[10] Another example focuses on the development of a microbe to harness and maximize the utility of renewable resources such as corn, sugar cane, and cellulose. ''The key to realizing these benefits…is a highly productive and efficient microbe able to use renewable sources of carbon and energy…in a commercial bioprocess. A microbe that meets these criteria for BioAcrylic has not been found in nature, so OPXBIO is applying proprietary EDGE™ (Efficiency Directed Genome Engineering) technology to redesign a natural microbe to achieve these goals.''[10]

Synthetic biology is now used fairly extensively to manufacture pharmaceuticals. For example, the anti-malaria drug artemisinin is based on artemisinic acid, a synthetic biology product that accelerates the production of vaccines. According to the JCVI report, ''[u]sing synthetic biology methods, vaccinologists will be able to construct specific vaccine seed viruses rapidly, cutting weeks or perhaps months from the current interval between virus identification and vaccine availability.''[1]

US Regulation of Synthetic Biology: An Overview

Based on the foregoing, a fair question to ask at this point is whether there is a fundamental difference between biotechnology and synthetic biology, as both seem to involve the genetic manipulation of organisms. According to the JCVI report, the ''underlying principles for synthetic biology are the same as those for more traditional recombinant DNA (rDNA) techniques, the biggest differences are in the size, scope, accuracy, and speed of genetic changes that can be accomplished.''[1] The JCVI report goes on to state that ''[a]s gene synthesis becomes cheaper and gene circuits…become better understood, a wider variety of complex organisms will become much more easily attainable; this advancement is already apparent in research settings and has started penetrating the marketplace.''[1]

As a subset of biotechnology, synthetic biology will both greatly enable and enhance technological advancements in genetic engineering and expand and diversify the cohort of scientists with the understanding needed to use these new scientific tools. These advancements are not abstractions and are having an immediate, real world impact: products of synthetic biology are being made and commercialized by greater numbers of entities, and at a faster pace than ever before. How the federal government and industry stakeholders are responding to this new reality is less clear.

The domestic regulation of synthetic biology falls within the domain of the Coordinated Framework for Regulation of Biotechnology, ushered into use in 1986 by the Reagan Administration's White House Office of Science and Technology Policy (OSTP).[11] The core premise of the Coordinated Framework was that existing legal authorities (which are essentially the same as those today) provide federal regulators sufficient authority to manage any health or environmental risk posed by products of biotechnology. 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 stands in stark contrast to the European Union's (EU) approach based on the Precautionary Principle, which is perhaps especially restrictive when applied to emerging technologies, the risks of which tend to be inherently more uncertain than those of more mature technologies.

Three federal agencies are principally responsible for regulating products of biotechnology: the EPA, the US Food and Drug Administration (FDA), and the US Department of Agriculture (USDA), and in particular its Animal and Plant Health Inspection Service (APHIS). APHIS is responsible for regulating field trials of genetically modified crops and plants under the Plant Pest Act. The 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). The 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, pursuant to what legal authority, and when in the

commercialization process varies considerably. We do not offer here a detailed discussion of the Coordinated Framework, or speculate as to its utility, strengths, and weaknesses. The JCVI report contains a useful Appendix that describes the legal authority for products of biotechnology under the Coordinated Framework.[1] It identifies important distinctions between and among the federal laws with jurisdiction over products of biotechnology regarding pre-market and post-market legal authority, organized by product. The remainder of this article focuses narrowly on the EPA's oversight under TSCA of synthetic biology products, as many near-term uses of synthetic biology, including biofuel production, are subject to TSCA.

TSCA and the Regulation of Synthetic Biology

The EPA regards synthetic biology as a form of biotechnology and uses its TSCA authority to regulate genetically engineered microorganisms used for non-pesticidal purposes, and which are not otherwise regulated under other federal authorities. The EPA has broad authority under TSCA to regulate the manufacture, use, distribution in commerce, and disposal of ''chemical substances and mixtures.''[12,13] The definition of a chemical substance is broad and includes ''any organic or inorganic substance of a particular molecular identity.''[14–17] The term chemical substance, as defined, does not include pesticides, drugs, or food, which are regulated under other federal laws.[18,19] The EPA issued regulations implementing its review of ''intergeneric microorganisms'' (which include bacteria, fungi, algae, viruses, and protozoa formed by combining genetic material from organisms in different genera) under TSCA in 1997.[20] More recently, the EPA has stated that chemically synthesized genes can be considered to be intergeneric, thus clarifying that microorganisms created via synthetic biology can fall within the scope of these regulations.[21] When defining the term 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. The sections below describe key TSCA provisions, starting with TSCA Section 2, which makes clear that the law is not intended to impede technological development, and Section 5 and the EPA regulations implementing this Section, which relate to new microorganisms.

TSCA SECTION 2

TSCA Section 2(b) discusses the policy of the US regarding actions under TSCA, including the need for adequate test data to be developed on the effects of chemicals (and that industry is responsible to perform such testing), that adequate regulatory authority should exist to control chemicals presenting ''unreasonable risks'' to health and the environment, and that this authority ''should be exercised in such a manner as not to impede unduly or create unnecessary economic barriers to technological innovation while fulfilling the primary purpose of this [Act] to assure that such innovation and commerce in such chemical substances and mixtures do not present an unreasonable risk of injury to health or the environment.''[22,23]

TSCA Section 2(c) states that it is the intent of Congress that, in implementing TSCA, the EPA ''shall consider the environmental, economic, and social impact'' of any actions taken.[24,25] Read in combination, TSCA Sections 2(b) and (c) make clear that in taking action to control unreasonable risks under TSCA, the EPA is to consider and balance the risks, costs, and benefits presented. (TSCA, like its federal counterpart law that regulates agricultural chemicals, is a risk-benefit statute, meaning that the EPA is required to balance the regulatory costs versus the likely benefits of a chemical regulation. More traditional environmental statutes such as the Clean Air Act and Clean Water Act do not require such balancing.)

TSCA SECTION 5

Under TSCA Section 5(a), persons must submit a notice to EPA at least 90 days prior to the manufacture, import, or processing of a new chemical substance for a commercial purpose or prior to the commercial manufacture, import, or processing of a chemical substance for a significant new use.[26] Microorganisms are included in the TSCA Section 3 definition of a chemical substance and are subject to all the provisions of TSCA, with limited exceptions.[27–32] The EPA started a screening program for microbial products of biotechnology in 1986 and, in 1997, issued comprehensive regulations fully implementing this program (See ''Microbial Products of Biotechnology: Summary of Regulations under the Toxic Substances Control Act'').[21] The EPA's regulations regarding microorganisms are codified at 40 C.F.R. Part 725. These regulations are comprehensive and include certain exemptions (including for commercial research and development, test marketing, and manufacture and use in contained systems). Unless the activity qualifies for an exemption, they require that manufacturers, importers, and processors submit a Microbial Commercial Activity Notification (MCAN) to the EPA at least 90 days prior to the manufacture, import, or processing of a new microorganism for a commercial purpose or for a significant new use.[33–35] If an MCAN is submitted and not needed, the EPA will notify the submitter.[34]

COVERED MICROORGANISMS

New microorganisms, like new chemical substances, are those not included in the TSCA Inventory.[36–38] If it is not possible to determine if a microorganism or use is listed on the Inventory, the regulations outline procedures that persons intending to conduct activities involving microorganisms should use to determine their obligations.[25,26] Under the regulations, either an exemption or an MCAN is required under TSCA Section 5(a)(1)(A) for new microorganisms that are intergeneric.[39] Microorganisms that are not intergeneric are automatically included on the Inventory.[40] Further, manufacturers, importers, or processors required to file an MCAN for research and development (R&D) activities may instead file a TSCA Experimental Release Application (TERA) for a specific test under certain situations.[41]

The regulations define a 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 Rhodophyta of the Plantae, and a virus or virus-like particle.''[36] An intergeneric microorganism is a microorganism formed by the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera.[36] As defined, it includes ''a microorganism which contains a mobile genetic element which was first identified in a microorganism in a genus different from the recipient microorganism,'' and it does not include ''a microorganism which contains introduced genetic material consisting of only well-characterized, non-coding regulatory regions from another genus.'' The EPA has clarified that microorganisms created through synthetic biology (chemically synthesized genes) can be considered intergeneric.

MANUFACTURE, IMPORT, OR PROCESS FOR COMMERCIAL PURPOSES

Under the regulations, the phrase manufacture, import, or process for commercial purposes is defined as follows:

> (i) To import, produce, manufacture, or process with the purpose of obtaining an immediate or eventual commercial advantage for the manufacturer, importer, or processor, and includes, among other things, ''manufacture'' or ''processing'' of any amount of a microorganism or microbial mixture
> (i) For commercial distribution, including for test marketing
> (ii) For use by the manufacturer, including use for product research and development or as an intermediate (a term that includes ''substances that are produced coincidentally during the manufacture, processing, use, or disposal of another microorganism or microbial mixture, including byproducts that are separated from that other microorganism or microbial mixture and impurities that remain in that microorganism or microbial mixture. Byproducts and impurities without separate commercial value are nonetheless produced for the purpose of obtaining a commercial advantage, since they are part of the manufacture or processing of a microorganism for commercial purposes.''[36])

According to EPA guidance, whether an activity has an ''immediate or eventual commercial advantage is determined by indicia of commercial intent.''[38] Some R&D activities are considered to be for commercial purposes, and thus subject to reporting. In particular, for example, if tests are directly funded, in whole or in part, by a commercial entity, or if the researcher intends to obtain an immediate or eventual commercial advantage, they may be construed as being for commercial purposes. Further, all post-R&D activities are considered manufacture or processing for a commercial purpose.

EXEMPTIONS

Exemptions from MCAN requirements include the following: an R&D exemption such as a TERA for R&D activities conducted outside a structure; the Tier I or Tier II exemption for manufacture and use in contained systems; and a Test Marketing Exemption Application (TMEA). If a notifier can satisfy the criteria and requirements for any of these exemptions, it may, depending on the particular exemption, commence manufacture or importation without notifying the EPA (in the case of R&D activities conducted ''inside a structure,'' as discussed further below) or may obtain expedited EPA review (e.g., a 45-day review for a TMEA rather than a 90-day MCAN review).

As an initial matter, TSCA Section 5(h) and EPA regulations do not allow an MCAN exemption application to be granted unless the EPA can determine that the microorganism ''will not present an unreasonable risk of injury to health or the environment.''[43,44] A manufacturer or importer seeking any MCAN exemption must submit to the EPA a Letter of Application that provides specific types of information:[45]

- Effects of the new microorganism on health and the environment
- Magnitude of exposure of human beings and the environment to the new microorganism
- Benefits of the new microorganism for various uses and the availability of substitutes for such uses
- Reasonably ascertainable economic consequences of granting or denying the exemption

In addition, the EPA requires the submission of information specific to the particular exemption being sought, as described further below. For the EPA to make a determination of unreasonable risk, it must balance the ''harm to health or the environment that a chemical substance may cause and the magnitude and severity of that harm, against the social and economic effects on society of EPA action to reduce that harm.''[46] The determination under TSCA is thus a risk-benefit calculus.

Research and development (R&D) exemption. The EPA provides an exemption from reporting requirements for R&D activities involving microorganisms. In the preamble to the final rule setting forth the microorganism regulations, the EPA expressed concern about R&D activities with microorganisms, rooted in the EPA's belief that living microorganisms may ''reproduce and increase beyond the number initially introduced, may establish in the environment, and may spread beyond the test site.''[47] The EPA provided two types of R&D exemptions. The first exemption, which does not require the submission of a Letter of Application, 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.''[42,48] This exemption requires the applicant to satisfy certain specific conditions, and if they meet these requirements, R&D activities may commence without the need for a Letter of Application to the EPA.

For R&D activities that do not qualify for the contained structure exemption, the EPA requires the submission of a TERA. The TERA seeks information identical to the information required in an MCAN—detailed information on the proposed R&D activity and information on monitoring, confinement, mitigation, and emergency termination procedures.[49] The TERA must also include data relating to a new microorganism's health

or environmental effects that are in a submitter's possession or control.[42,50] The submitter must provide this information to the extent that it is ''known to or reasonably ascertainable by the submitter.''[50] Submission of TERAs must take place at least 60 days before the initiation of the proposed R&D activities.[51]

If the EPA determines that the proposed R&D activity for the microorganism ''will not present an unreasonable risk of injury to health or the environment,'' the EPA will so notify the submitter and the submitter may proceed with the proposed activity as specified in the TERA.[52] If, however, the EPA concludes that it cannot reach such a determination and rule out unreasonable risk from the R&D activity, then it will deny the TERA and provide reasons for its denial in writing.[52]

Tier I and Tier II Exemptions. The EPA has established a two-tiered exemption process from MCAN requirements for microorganisms that meet specified criteria. To qualify for the Tier I exemption from MCAN requirements:

- The microorganism must be one of ten species (*Acetobacter aceti, Aspergillus niger, Aspergillus oryzae, Bacillus licheniformis, Bacillus subtilis, Clostridium acetobutylicum, Escherichia coli K-12, Penicillium roqueforti, Saccharomyces cerevisiae,* or *Saccharomyces uvarum)* and must meet introduced genetic material criteria (i.e., limited in size, well-characterized, poorly mobilizable, and free of certain toxin-encoding sequences)[53]
- 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
- The manufacturer or importer must comply with record-keeping requirements[54]

The Tier II exemption also provides for an expedited review of microorganisms that satisfy Tier I requirements, except for the requirement that the facility meet all necessary physical containment and control technology requirements.[55] Manufacturers and importers must submit to the EPA a Tier II exemption application at least 45 days prior to commencing initial manufacture or import of the new microorganism.[56] The EPA will approve or deny the Tier II exemption request no later than 45 days after it receives the request.[57]

Test Marketing Exemption Application (TMEA). In lieu of complying with MCAN requirements, persons may submit a TMEA.[58,59] 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.''[38] The EPA suggests that manufacturers who intend to test market a new microorganism file an MCAN rather than request a TMEA.[38] According to the guidance, a TMEA may be appropriate in limited situations, such as for microorganisms that the EPA had previously reviewed at the R&D stage.[38] In addition to the general requirements for an exemption request, as discussed above, the application must be submitted at least 45 calendar days before commencement of the test marketing activity.[60]

Technical information to be included in the TMEA includes ''all information known to or reasonably ascertainable by the person on the microorganism and the test marketing activity…that the person believes will demonstrate that the microorganism will not present an unreasonable risk of injury to health or the environment as a result of the test marketing.''[61] The TMEA must include at least the following information:

- An explanation of why any required information is not available or not applicable
- The submitter identification and microorganism identity information required for MCANs
- Relevant phenotypic and ecological characteristics information
- Certain information about the proposed test marketing activity[38,61]

The EPA will either approve or deny a TMEA no later than 45 days after receipt, and may impose restrictions with approval.[62] The submitter ''may only proceed with test marketing activities after receipt of EPA approval.''[62]

MCAN REQUIREMENTS

The procedure for submitting an MCAN and the information required for inclusion in such an application are outlined generally below.

Timing. An MCAN must be submitted at least 90 calendar days prior to manufacturing or importing a new microorganism or manufacturing, importing, or processing a microorganism for a significant new use.[63] The submitter can request a suspension of the review period, if necessary, although the EPA can refuse.[64] Similarly, the EPA can extend the review period for ''good cause,'' as described in the regulations.[65] Submitters can also withdraw submissions.[66]

Within 30 days of receipt of the submission, the EPA may request that the submitter remedy errors in the submission and if the errors are not corrected within 15 days, the EPA may extend the review period.[67] Errors may include failure to date the submission, typographical errors that cause data to be misleading, answers to questions to be unclear, or information to be contradictory, and ambiguous statements or information. Similarly, if a submission is incomplete, the review period does not begin.[68] Examples of incomplete submissions include a wrong filer, no certification statement, information or attachments not in English, missing information, and failure to follow confidentiality claim procedures or to pay fees.

The EPA will notify the submitter that the MCAN review period has expired or that the EPA has completed its review of the MCAN.[69] Expiration of the review period does not constitute EPA approval unless EPA takes certain actions. The submitter may, however, ''manufacture or import the microorganism even if the submitter has not received notice of expiration'' once the period—including any extensions or suspensions—expires.[70] The regulations state the following: ''No person submitting a MCAN in response to the requirements of this subpart may manufacture, import, or process a microorganism subject to this

subpart until the review period, including all extensions and suspensions, has expired.''[71]

Such new microorganisms will be added to the Inventory once EPA receives a Notice of Commencement (NOC) indicating that manufacture or importation has actually begun.[72] In its guidance, EPA recommends that persons planning to submit MCANs (as well as certain other types of submissions) ''discuss their plans in advance'' with a Biotechnology Program Manager in the New Chemicals Management Branch.[38]

Main elements of MCAN submission. Unlike the TSCA Premanufacture Notification (PMN) process for industrial chemicals, there is no specific EPA form to be used for this submission. The regulations specify what information to provide, including the following, and the EPA guidance provides further detail and a suggested data submission format.[26,58]

- *Microorganism Identity Information:* Persons must submit sufficient information to allow the microorganism to be accurately and unambiguously identified for listing purposes. This includes:[38,73]
  - Description of the recipient microorganism and the new microorganism
  - Genetic construction of the new microorganism
  - Phenotypic and ecological characteristics[38,74]
- *Byproducts*: A description of the byproducts resulting from the manufacture, processing, use, and disposal of the new microorganism[75]
- *Total Production Volume*: The estimated maximum amount of the new microorganism intended to be manufactured or imported during the first year of production and the estimated maximum amount to be manufactured or imported during any consecutive 12-month period during the first 3 years of production. This estimate may be by weight or volume and should include an estimation of viability (i.e., viable cells per unit volume or colony forming units per unit dry weight)[38,76]
- *Use Information*: A description of intended categories of use by function and application, the estimated percentage of production volume devoted to each category of use, and the percentage of the new microorganism in the formulation for each commercial or consumer use[77]
- *Worker exposure and environmental release (a broad range of information is requested, including substantiation of the taxonomic classification of the new organism; a detailed description of the process of construction, a description of the new microorganism's habitat and geographical distribution, and the source of the recipient microorganism; survival and dissemination under relevant environmental conditions and methods for detecting the new organism in the environment; and a description of anticipated biological interactions with multiple other organisms and of involvement in biochemical or biological cycling processes):* For sites controlled by the submitter, this includes:
  - The identity of sites where the new microorganism will be manufactured, processed, or used
  - A process description of each manufacture, processing, and use operation
  - Worker exposure information
  - Information on release of the new microorganism to the environment
  - A narrative description of the intended transport of the new microorganism
  - Procedures for disposal of any articles, waste, clothing, or other equipment involved in the activity

For sites not controlled by the submitter, the required information includes a description of each type of processing and use operation involving the new microorganism, including identification of the estimated number of processing or use sites, situations in which worker exposure to and/or environmental release of the new microorganism will occur, the number of workers exposed and the duration of exposure; procedures for transport of the new microorganism and for disposal, including procedures for inactivation of the new microorganism; and control measures that limit worker exposure and environmental release.[38,78]

An MCAN submission must include the above information ''to the extent such information is known to or reasonably ascertainable by the submitter.'' Further, the submission must also include any test data in the submitter's possession or control and descriptions of other data that are known to or reasonably ascertainable by the submitter and that concern the health and environmental effects of the microorganism.[79]

EPA REVIEW AND REGULATION OF NEW MICROORGANISMS

The EPA will review the information submitted in the exemption application or the MCAN, along with other available information, to assess the potential hazards, exposures, and risks associated with the microorganism. In the case of exemption applications, the EPA's review will focus on determining whether to grant or deny the application based on its ability to make and support a ''will not present an unreasonable risk'' determination. For MCANs, the EPA's review focuses on determining the potential for the new microorganism to present unreasonable risks and/or to identify microorganisms that may have significant new uses. The discussion to follow focuses on the review of MCANs; the assessment approaches used are also applied to exemption applications as appropriate.

The EPA review begins with consideration of the information provided in the MCAN and includes any other relevant information available to the EPA, which can include information received by the EPA on other related microorganisms. This includes evaluation of the following:[38]

- The new microorganism with specific focus on the details of the recipient organism, the donor organism, or the chemically synthesized genetic material, and the final construct focusing on the intergeneric DNA and the intrageneric DNA that affects the expression, stability, and mobility of the intergeneric DNA
- Any submitted test data on the identity, survival, adverse effects, and related factors of the new microorganism
- Predicted or identified health and environmental effects of the new microorganism, including pathogenicity, virulence,

or infectivity to other organisms, toxicity of microbially produced toxins, and related considerations
- Natural habitat and geographical distribution of recipient microorganisms; comparison of survival and other fate aspects of the modified and parental strain microorganism in soil and water samples from known or release site; survival/persistence of modified organism in environmental media other than release site; prevalence of gene exchange in natural populations, methods of detection, and related considerations
- Production volume, byproducts, and uses
- Worker, consumer, and environmental exposures
- Control/containment technology and information on releases during manufacture, processing, and use
- Information applicable to field tests

The EPA can take any of a variety of regulatory actions under TSCA Section 5(e) to control the manufacture, uses, volumes, releases, and related aspects if evidence exists to support certain determinations. The most important of these for purposes of a new microorganism is to determine if it may present an unreasonable risk to health or the environment. A determination of unreasonable risk involves assessment of the hazards and exposures associated with the microorganism's manufacture, processing, use, or disposal, and includes consideration of cost-benefit and relative risk factors. If the EPA concludes that the new microorganism may present an unreasonable risk, it can prohibit or limit commercial activities (e.g., limit production volumes or uses, control worker exposures, limit or prohibit releases to the environment, or impose other control measures) pending development of test data needed to support a reasoned evaluation of the risks. In these cases, the EPA will typically require the notifier to conduct testing needed to address areas of uncertainty that could further the risk assessment, including, for example, additional characterization of the new microorganisms and/or the genetic construct, toxicity aspects, effectiveness of control technology, kill rates, survival in environmental media, and monitoring, among other factors dictated by the nature of the proposed application.

Alternatively, or in addition, the EPA, under TSCA Section 5(a)(2), can regulate significant new uses of microorganisms following consideration of a series of factors. Once promulgated, such rules would require submission of an MCAN to the EPA prior to initiating any such significant new use. The EPA would review this information in a similar manner to that described above, although its review would focus specifically on the risks presented by the significant new use. A person that submits a Section 5(a) notice must submit an NOC of manufacture or import of a new microorganism for non-exempt, commercial purposes to the EPA no later than 30 calendar days after the first day of such manufacture or import, but not prior to manufacture or import.[80]

Experience to Date Under TSCA's Biotechnology Regulation

Based on information provided by the EPA on its website or otherwise obtained from the EPA, since promulgation of the microorganism rule in 1997 through 2013, the Agency received a total of 118 Tier I and two Tier II exemption requests, one TMEA, 29 TERAs, and 55 MCANs (personal communication, James Alwood, EPA Office of Pollution Prevention and Toxics (OPPT), Chemical Control Division).[81,82] (Additional Tier I applications were received in 2012; the total number is not available.) Of these totals, the EPA granted all Tier I, Tier II, and TMEA requests and 28/29 (97%) of TERAs. It did not further regulate 53 (96%) MCANs: one was subjected to a Significant New Use Rule (SNUR); one was regulated via a Consent Order under TSCA Section 5(e), and one MCAN was withdrawn by the submitter. Accordingly, approximately 5% of MCAN cases have been regulated by EPA or have been withdrawn by the submitter.

MCANs that enter commerce are required to have an accompanying NOC; the EPA has received NOCs for 22 (36%) of the MCANs notified. Information on TERAs and MCANs for the period 1998–2013 is summarized in *Table 1*. By way of contrast, the EPA has received more than 36,000 under TSCA since 1979 and, of these, approximately 10% have been regulated/withdrawn, and NOCs have been received on about 50% of the new chemical notifications on record.[83]

Consideration of these statistics indicates that the EPA has consistently received a small number of MCANs each year. This number has started increasing over the past several years. For example, over the period 1998–2010, the EPA received 35 MCANs (about 2.7/year), while from 2011–2013, the Agency received 20 MCANs (about 7/year).

Importantly, the overwhelming majority of exemption requests (including Tier I and Tier IIs, TMEAs, and TERAs) and MCANs have either been granted by the EPA or not been regulated via Consent Orders or SNURs, respectively. The consistency of this pattern over time is an important factor that should be recognized by companies, and provides a comforting statistic for entities considering development and commercialization of new microorganisms. At the same time, companies should consult the information available on the notified microorganisms when preparing to commercialize a new microbe, as

Table 1. TERA and MCAN Submissions and Regulatory Outcome (1998–2013)

SUBMISSIONS RECEIVED	
MCAN	55 (average/y ~3.4; received 20 MCANs or ~7/y between 2011–2013)
TERA	29
Total Received	84 (5.3/y; received 27 MCANs and TERAs, or ~9/y, between 2011–2013)
REGULATORY OUTCOMES	
MCANs with no EPA regulatory action	52
MCANs withdrawn/section 5(e) order/SNUR	3 (5%)
MCANs with NOC	22 (36%)
TERAs approved	28 (97%)

these results may offer insights reflective of key specifics related to the species involved (such as pathogenicity), the nature of the genetic change, containment, survival characteristics, and related considerations. Regarding the recent uptick in usage information, this is seemingly attributable to biofuels development and commercialization (personal communication, James Alwood, July 23, 2014).

Thoughts on How to Maximize TSCA's Adaptive Capacity to Enhance the Sustainable Commercialization of Synthetic Biology Products

Because synthetic biology applications achieving commercialization are concentrated in the biofuels and biobased chemicals production areas, the EPA is likely to experience a continuing uptick in MCANs. The statistics presented in the previous section confirm such an increase, with more than a doubling of MCANs received by the EPA over the period 2011–2013 compared to earlier years. The MCANs appear to relate to biofuels, renewable chemicals, and industrial enzyme production (personal communication, James Alwood, July 23, 2014).[3] An important point to consider from industry's perspective is the overwhelmingly positive response by the EPA to the exemption requests and MCANs, with most cases either being granted or essentially ''approved'' for commercialization, respectively. This result may reflect a careful approach by companies in commercializing new microorganisms, both in their selection of the parent organism and the final genetic construct. This result also may reflect favorably on companies' efforts to minimize the potential for release of and exposure to the microorganisms, and, presumably, appropriate attention to survival issues in the environment. This commitment to careful planning speaks highly of this growing industry.

Based on our experience in working with industry clients as well as our understanding of EPA's needs and expectations, we offer the following points for consideration by companies active in this area:

- Ensure that TSCA compliance is a core element of the business plan: knowing and understanding TSCA requirements is essential. TSCA provisions should not be collateral to any business' strategic plan; they must be a core element embedded in the planning process. A good command of TSCA will decrease the likelihood of a major, unanticipated disruption to the commercialization timeline due, for example, to late recognition of the need for an MCAN or other significant new chemical issue. A strong compliance program will also help avoid EPA enforcement issues and the significant potential costs (both monetary and reputational) that can result. (According to EPA policy, for example, each day of production or importation of a new chemical substance in violation of TSCA Section 5 PMN requirements constitutes a new violation, for which the penalty can be as high as $37,500, depending on the type and quantity of the substance.)[84,85]
- Work with the EPA: It is imperative to consult with the EPA before embarking on developing a new microorganism. Notification and/or a testing strategy should be developed in consultation with EPA staff to ensure an understanding of the EPA's views on this proposed approach and to obtain EPA receptivity to the approach.
- Ensure that the EPA is aware of scientific innovations and commercial developments: Synthetic biology professionals in the private sector should create opportunities to brief EPA scientists and regulators on innovations and technological developments. It is critically important that the private sector enhance and expand its efforts to share information with the EPA to ensure that Agency personnel are aware of key developments, and to engage with the EPA regarding issues and concerns, and thus give the EPA timely awareness of and the opportunity to think through the science policy and regulatory implications of these developments, issues, and concerns. Individual companies are also encouraged to consider the benefits of meeting separately with the EPA to build confidence and increase mutual understanding while protecting important commercial information.
- Solve the EPA funding problem: OPPT is and has been chronically underfunded.[86] Despite the open-ended nature of the EPA's mandate under TSCA, the Agency depends entirely on Congress' generosity for funding. There is no fee for service program as there is under the Federal Food, Drug, and Cosmetic Act (FFDCA) or FIFRA, and OPPT's reliance on ever-shrinking resources presents an almost insurmountable problem for EPA management to get ahead of the curve, anticipate, and creatively address new challenges posed by evolving technology while meeting TSCA's other goals and objectives.

Conclusions

The experience to date under the TSCA biotechnology program has been positive, although it is only now that the rate of submissions is ticking up, perhaps as a reflection of the new techniques and technologies provided by synthetic biology, as well as the emerging importance of biofuels and renewable chemicals. This is good news for this important sector of the economy and, particularly because of these developments, there is a need for and value in greater understanding and transparency regarding this TSCA program. For example, the information on the EPA's website, while useful, is limited in its scope and depth of coverage and analysis, and the EPA is encouraged to provide more and more useful information. The web-accessible information, for example, could be expanded to include case studies that reflect the experience collected over nearly two decades since the rule was implemented, new guidance question and answer documents, and related information. Such case studies would assist in educating stakeholders regarding this important but relatively invisible program (further to this point, we would note that the EPA's ''Points to Consider'' document dates to 1997 and would benefit from a comprehensive update[38]). Industry is also encouraged to consider steps it might take to do a better job of informing and educating the EPA and the public about technological innovation. There may be value in considering and realizing opportunities for public dialogue and discussion in this area, including learning more about the EPA's experience in implementing its biotechnology regulation and its future plans and needs, industry's views in these regards, some

indication of the EPA's future expectations, and to hear the views of other stakeholders.

Such an opportunity would also provide a platform to increase understanding about the need for increased Agency resources to review and assess these notifications in a manner that is both timely and thorough. Recognizing that the EPA's budget is at the mercy of Congress, the prospects for adequate resourcing are not encouraging. This means that stakeholders should be encouraged to work creatively and hard to ensure that EPA resource and staffing deficits do not blunt commercialization prospects, while also ensuring careful review of the products of this important emerging technology.

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14. TSCA § 3(2)(A).
15. 15 U.S.C. § 2602(2)(A).
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17. 40 C.F.R. § 720.3(e).
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25. 15 U.S.C. § 2601(c).
26. 15 U.S.C. § 2604(a)(1).
27. 15 U.S.C. § 2602(2).
28. 62 *Fed Reg* 17910, 17911 (Apr. 11, 1997).
29. To the extent that such microorganisms are excluded from the definition of chemical substance by TSCA Section 3, they are not subject to these requirements. The term chemical substance excludes mixtures; "any pesticide…when manufactured, processed, or distributed in commerce for use as a pesticide"; tobacco or any tobacco product; certain nuclear materials; certain firearms; and "any food, food additive, drug, cosmetic, or device…when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device." TSCA § 3(2).
30. 15 U.S.C. § 2602(2).
31. 40 C.F.R. § 720.3(e).
32. 40 C.F.R. § 725.8.
33. 40 C.F.R. § 725.150.
34. 40 C.F.R. § 725.28.
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41. 40 C.F.R. § 725.1(c).
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43. 15 U.S.C. § 2604(h).

44. 40 C.F.R. § 725.67(a), (b).

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47. 62 *Fed Reg* at 17923.

48. 40 C.F.R. § 725.234(d). 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 § 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."

49. 40 C.F.R. § 725.255.

50. 40 C.F.R. §§ 725.260.

51. 40 C.F.R. § 725.250.

52. 40 C.F.R. § 725.270(b).

53. 40 C.F.R. § 725.420.

54. 40 C.F.R. § 725.424.

55. 40 C.F.R. § 725.428.

56. 40 C.F.R. § 725.450(b).

57. 40 C.F.R. § 725.470(e).

58. 40 C.F.R. § 725.300.

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