TSCA Affects on Algae, Other Novel Biosources, and Bioprocesses

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Introduction

The Toxic Substances Control Act (TSCA) is the federal gap-filling chemical control law regulating chemical substances used in applications other than food, drugs, cosmetics, and pesticides, and other uses that are regulated by other federal authorities. Chemical product innovators need to understand how TSCA, significantly amended in 2016, applies to biomass starting material, including industrial microorganisms (such as algae), intermediates, and commercial products, and build TSCA compliance into business timelines and budgets. Doing so will better assure uninterrupted business operations and consistent TSCA compliance.

The products made by and from industrial microbes and algae have the potential to reduce toxicity, greenhouse gas (GHG) emissions, and dependence on non-renewable resources. These microorganisms can be used to manufacture a wide variety of products, including fuels and fuel additives, chemicals, materials, food, and feed. To ensure these products successfully enter the market, it is critical for companies that manufacture microorganism-based products to understand and comply with TSCA and the Federal Food, Drug, and Cosmetic Act (FFDCA). Since 1997, the U.S. Environmental Protection Agency (EPA) has considered intergeneric microorganisms to be new chemical substances regulated under TSCA.[1] Microorganisms created from chemically synthesized genes can be considered intergeneric if the synthetic sequence is not identical to the genetic sequences found within the organism's genus.[2]

TSCA Fundamentals

Acompany can comfortably operate under the TSCA Section 5(h)(3) research and development (R&D) exemption while it develops the technology required to manufacture its product.[3] The exemption allows entities conducting R&D activities to avoid obtaining pre-market approval of their R&D chemical substances. The exemption no longer applies, however, once the new chemical innovation is ready for commercial launch. At that time, the company must comply with all aspects of TSCA to remain compliant and avoid costly business interruptions, potentially significant fines, and reputational damage. TSCA compliance is required for the final commercial product, as well as the feedstocks, microorganisms, intermediates, catalysts, and enzymes used throughout the production process that are not otherwise TSCA exempt.

Although TSCA was significantly amended by enactment of the Frank R. Lautenberg Chemical Safety for the 21st Century Act on June 22, 2016, a key provision regarding the TSCA Inventory was preserved. New TSCA still requires that all chemical substances manufactured in or imported into the U.S. for TSCA purposes to be listed on the TSCA Inventory or to be eligible for an exemption. Importantly, there are two portions of the TSCA Inventory: the public portion that lists specific identities; and a confidential portion that lists generic identities. To determine whether a chemical substance is listed on the confidential portion of the Inventory, a company with a valid commercial need can submit a *Bona Fide* Intent to Manufacture or Import Notice (BFI) to EPA to obtain written confirmation on the TSCA status of the substance.

New TSCA Substances

If a chemical substance, in this case a microbial substance, is not listed on the TSCA Inventory, it is considered a new substance and the manufacturer or importer is required to notify EPA at least 90 days prior to manufacturing or importing the chemical substance for a non-exempt TSCA purpose.[4] For microorganisms, EPA requires notification in the form of a Microbial Commercial Activity Notice (MCAN), which includes information on the following aspects of the microbe:

- Identity;
- Byproducts from the manufacture, processing, use, and disposal of the microorganism;
- Anticipated uses and production volume;
- Available test data;
- Expected environmental release and worker exposure from manufacturing, processing, and use; and
- Starting materials and manufacturing process (if applicable).[5–8]

Bioeconomy companies are also encouraged to include optional pollution prevention information to emphasize the benefits of the new chemical, including the use of renewable resources and safer processes, reduced pollution, avoidance of toxic intermediates, and toxic waste generation. In addition to data from the submitter, EPA considers other information in its risk assessment for the substance, including information on analog substances, quantitative structure-activity relationship (QSAR) analyses when hazard data are not available, and conservative assumptions about potential exposures and releases if sufficient information is not provided by the submitter. All MCAN submissions must be accompanied by a modest fee, the amount of which is subject to

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increase following an anticipated EPA rulemaking pursuant to new TSCA.[9]

Under new TSCA, EPA must publish a notice in the *Federal Register* announcing the receipt of each MCAN and exemption submission and its affirmative determination for each MCAN submission.[10] Following its review of the available data, EPA must make one of five determinations regarding the risk of the microorganism to human health and the environment before the submitter can initiate the desired commercial activity. EPA may determine that:

- The chemical substance presents an unreasonable risk;
- The chemical substance may present an unreasonable risk;
- There is insufficient information to make a reasoned evaluation;
- The chemical substance may enter the environment in substantial quantities or there may be significant or substantial exposure to the substance; or
- The chemical substance is not likely to present an unreasonable risk.[11]

It is critical that MCAN submitters understand the considerations that constitute EPA's review of new microorganisms and provide the relevant information to the extent that it is known or reasonably ascertainable. Without confidence that it has sufficient information, EPA is required by new TSCA to take regulatory action to protect against potential unreasonable risks. In addition to expanding on the information provided in the MCAN submission, EPA has the authority under new TSCA to consider the ''reasonably foreseen'' ''conditions of use'' of a microorganism beyond those specified in the MCAN.[12] Additionally, EPA is directed to consider ''potentially exposed or susceptible subpopulations,'' including children, workers, and the elderly, during its review.[13] Chemical product innovators working with algae and other microorganisms should carefully analyze EPA's ongoing implementation of new TSCA to determine its impact on the review of emerging biotechnology.

Naming Biobased Substances

When preparing a MCAN submission, it is critical that attention be paid to the substance identity, as it can affect the TSCA regulatory status of the substance and its downstream products. For substances with a single, well-defined chemical structure, such as ethanol and lactic acid, the naming conventions and TSCA Inventory search are straightforward. The precise determination of the chemical identity and TSCA Inventory status of a substance lacking a definitive molecular formula or structural diagram can be complicated. These complex substances, referred to as Class II chemicals or ''unknown or variable composition, complex reaction products, or biological materials'' (UVCB), are often identified by the source and chemical processes used during manufacturing. The source-based nomenclature system results in multiple nomenclature listings for nearly equivalent chemical substances that are derived from different sources. For example, palm, canola, and sunflower oil are each listed separately on the TSCA Inventory. Companies should also be aware that the Class II nomenclature system propagates through the supply chain, for example, if each of the palm, canola, and sunflower oils is converted to fatty acid methyl esters (FAME), the individual FAMEs are listed separately (e.g., fatty acid, sunflower, Me ester). This source-based system has significant business implications. It means that the manufacturer of a novel source chemical substance (e.g., algal oil) is required under TSCA to submit to EPA a premanufacture notice (PMN) to add the substance to the TSCA Inventory before commercializing the material. Importantly also, the manufacturer's customers may be required to submit PMNs for downstream UVCB substances that are produced from it, such as free fatty acids and biodiesel. The time and business planning that it takes to accomplish these inconvenient realities cannot be over-emphasized.

In 1979, EPA attempted to streamline the Class II nomenclature system by developing a source-agnostic system with the help of the Soap and Detergent Association (SDA) (now the American Cleaning Institute). The SDA nomenclature system, which is based on substance type and alkyl range rather than source and processing, allows for significantly expanded feedstock and operational flexibility by drawing equivalence between chemical substances produced from 35 natural sources of fats and oils and their petroleum-based counterparts, but limits eligibility to these sources.[14] Novel sources of oils (such as camelina, microbes, or algae) are not eligible regardless of whether they are genetically modified. The SDA system is closed to new sources. New TSCA provides EPA with authority to recognize multiple listings of a substance on the Inventory as a single substance. EPA is not mandated to exercise this authority, but discussions between industry and EPA are underway. To support the efficient commercialization of biobased products, the microbial chemical industry would be well advised to engage with EPA to ensure that consideration is given to a wider range of sources, not just the ones that were available in 1979. Expansion along these lines would facilitate operational flexibility and level the playing field for new product entrants that are based on natural sources that fall outside the listed 35 natural sources.

Reporting Exemptions

In addition to understanding the process for notifying commercial microbial activity, companies should be familiar with the reporting exemptions that are available. The previously mentioned R&D exemption under TSCA Section 5(h)(3) applies to activities conducted within a contained structure for a noncommercial purpose.[15] For certain R&D activities using an intergeneric microorganism outside of a contained structure, EPA requires the submission of a TSCA Environmental Release Application (TERA) at least 60 days prior to the activity.[16] EPA has established a two-tiered exemption that expedites the review process for commercial microorganisms that meet certain criteria.[17] The Tier I exemption is available for new microbes when the following requirements are met: (1) the microorganism is one of ten species identified in the regulations; (2) the introduced genetic material meets specific criteria (e.g., limited in size, well characterized, poorly mobilizable, and free of certain toxin-encoding sequences); (3) the facility in which the microorganism will be manufactured, processed, or used meets the physical containment and control technologies criteria; (4) a

certification is submitted to EPA at least ten days prior to commencing the manufacture or import of the new microorganism; and (5) the manufacturer or importer complies with recordkeeping requirements.

The Tier II exemption offers an expedited review of microorganisms that satisfy the Tier I requirements, aside from the physical containment and control technology requirements. A Tier II exemption application must be submitted to EPA at least 45 days prior to commencing manufacture or import of the new microorganism. The Section 5(h)(4) exemption applies to microorganisms that EPA determines ''will not present an unreasonable risk of injury to health or the environment.''[18]

Finally, companies performing test marketing activities involving microorganisms that are not going to be released to the environment may submit a test marketing exemption (TME) application.[19] Test marketing is defined as a process to enable the PMN submitter to focus on customers' acceptance of a chemical substance and the probable demand for a product in a market where it will ultimately be competing with incumbent products.

Naturally occurring substances are exempt from reporting since EPA considers such substances to be automatically listed on the TSCA Inventory.[20] EPA has defined ''naturally occurring'' substances narrowly, and care should be taken to understand its scope. Microorganisms that do not contain genetic material from organisms of a different taxonomic genus may be considered naturally occurring, whereas intergeneric microorganisms are not naturally occurring. Importantly also, the processing of a microbe or other biobased substance beyond the discrete methods described in the definition of naturally occurring substances likely results in a substance that EPA would not consider naturally occurring. Depending on their end use, intergeneric microorganisms, feedstocks, intermediates, byproducts, enzymes and other catalysts may be reportable under TSCA. Furthermore, companies that rely on byproducts or waste as a feedstock should engage with their supplier regarding the TSCA status of the feedstock to avoid undue supply delays. For example, yellow grease (waste glycerides from kitchen uses) is listed on the TSCA Inventory, so it may be used as a feedstock for growing microbes for a non-exempt TSCA purpose. Brown grease (waste glycerides from sewage treatment), however, is not listed on the Inventory, so EPA would be of the view that a bioeconomy company could not use brown grease as a feedstock for a commercial purpose regulated under TSCA.

Additional TSCA Provisions

The microbial chemical industry may also be interested in some of the more general provisions that were introduced as part of new TSCA. For instance, Section 14 now requires that companies substantiate many confidential business information (CBI) claims at the time the confidential information is submitted to EPA.[21] The substantial process takes time; careful consideration and a rigorous process must be part of the business process.

New TSCA also expands Section 14 to include new categories of information not protected from disclosure, including mixed confidential and non-confidential information, and general descriptions of the manufacturing and/or processing and aggregated production volumes.[22] Companies should also be aware that health and safety studies cannot be protected as CBI (although the identity of the test substances may be confidential). Additionally, new TSCA requires EPA to consult with the Small Business Administration (SBA) to review the adequacy of the current standards for small manufacturers and determine whether a revision of the definition of a ''small'' business is warranted.[23] Given that the sales thresholds that define what is deemed ''small'' for TSCA purposes have not been increased to keep pace with inflation, companies should expect the threshold to rise, thus expanding the protections afforded small businesses. Small businesses involved with microorganisms should consider monitoring or engaging in activities related to this provision.

Regulatory Guidance

To assist companies in navigating the regulation of substances under TSCA, EPA is required by new TSCA periodically to review and update the policies, procedures, and guidance regarding its assessment and determination of risk and consideration of new scientific developments or understandings. Over the years, several guidance documents have been developed for the biotechnology community and updates to some are expected in the near future. The ''Coordinated Framework for the Regulation of Biotechnology,'' updated in January 2017, outlines the principles for the regulation of biotechnology products, roles, and responsibilities of EPA, the U.S. Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA) with respect to regulating biotechnology products, the mechanisms in place for interagency communication and coordination, and the mechanism and timeline for updating the Coordinated Framework.[24]

EPA has stated that it is updating its ''Points to Consider in the Preparation of TSCA Biotechnology Submissions for Microorganisms'' document, which was developed in 1997 to include information relevant to the risk assessment of novel biotechnology products.[25] An updated version is required to provide useful guidance for today's emerging technologies regarding microorganism production and use.

In 2016, EPA published the ''Draft Algae Guidance for the Preparation of TSCA Biotechnology Submissions,'' which addresses the current scientific and technical issues facing the biotechnology algae and will likely inform the update of the Points to Consider document.[26] EPA intends to develop a ''Considerations for Biotechnology Algae'' document in conjunction with the update to the Points to Consider document, to increase the transparency of the review process and increase the likelihood that MCAN and TERA submitters receive expeditious EPA review of their submissions, while ensuring that commercialized products maximize their benefits to society by minimizing the potential risks to human health and the environment.

In February 2017, the Science Advisory Committee on Chemicals (SACC) was formed pursuant to new TSCA to provide peer review of risk assessments, models, tools, guidance documents, chemical category documents, and other chemical assessment

products.[27] Although its members include experts in toxicology, exposure, and environmental risk assessment and related sciences, it will be key for the biotechnology community to engage with SACC to ensure that regulatory developments related to microorganisms are scientifically sound and properly managed.

Conclusion

The full implications of new TSCA will become clearer as EPA implements its new authorities and EPA's deployments of these authorities are judicially refined. It is crucial that the microbial chemical industry is familiar with the statutory provisions and engages meaningfully and robustly in implementation activities that impact the development, regulation, and commercialization of algal products. A thorough understanding of EPA's approach to chemical regulation is key to avoiding commercial disruptions and operation delays, competitive imbalances, and potential assertions of noncompliance. Companies are encouraged to develop a strong compliance program, to consider the regulatory timeline when formulating business plans, and to seek assistance from experts in the regulatory and legal fields regarding the preparation and review of EPA submissions. Innovators are encouraged also to develop strong relationships with regulators based on trust and clear and open communication. Regulators are a critically important component of the stakeholder community and often under-appreciated as one of a businesses' strongest supporters. While EPA may recognize and be receptive to the benefits of biobased products, it is still required to regulate a biobased chemical substance if it determines that the substance may present unreasonable risk during the review process. Engaging with EPA early in the process to understand any potential concerns, how those concerns can be addressed, and how a product's pollution prevention attributes provide essential value to the economy may help companies avoid significant regulatory issues and potentially costly business delays down the road.

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