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WASHINGTON WATCH

Biotechnology: A Lot is Going On

By Lynn L. Bergeson

Biotechnology is an area of growing domestic and international importance to the manufacturing sector, and this summer the federal government announced several important biotechnology initiatives of which stakeholders should be aware. On July 2, 2015, the White House Office of Science and Technology Policy (OSTP), the Office of Management and Budget (OMB), the United States (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) (Holdren, Shelanski, Vetter, & Goldfuss, 2015a).

A few weeks later, EPA's Office of Pollution Prevention and Toxics (OPPT) announced a project intended to support public dialogue concerning the development and use of biotechnology—and to help advance public discourse on the topic of biotechnology—by developing a new algae "how to" document for Toxic Substances Control Act (TSCA) purposes (EPA, 2015a). Finally, the 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 initiatives is important, and they are all

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interrelated. This article explains each initiative, and outlines why stakeholders are encouraged to engage in each one.

Coordinated Framework for Regulation of Biotechnology

Many people think of biotechnology only within the context of food and agriculture. Industrial biotechnology is a significant component of this technology, however, and it applies biotechnology to industrial processes. Industrial biotechnology seeks to optimize biochemical features that can be used and applied in industrial processes to reduce pollution, minimize cost, and optimize nature's enzymes. Although the health care industry and agricultural communities have been using biotechnology for years, industrial biotechnology applications are increasing greatly, and the industrial sector is taking note.

The federal oversight of products of biotechnology is directed through the Coordinated Framework, which was issued in 1986 by the Reagan Administration's White House OSTP, and updated in 1992.[i] 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 core premise of the Coordinated Framework is that the legal authorities that existed in 1986, statutory authorities which remain largely unchanged, provide federal regulators sufficient authority to manage any health and/or environmental risk that products of biotechnology may pose.

The Coordinated Framework was intended to be a flexible governance construct capable of nimbly adjusting to new science and innovation and not

shackle legal authorities rigidly to specific biotechnology products. Risks are assessed on a case-by-case, product-by-product basis and focus on a product's application and its intended use, not on the technology itself.

Under the Coordinated Framework, three federal agencies are principally responsible for regulating products of biotechnology: the USDA, and in particular, the Animal and Plant Health Inspection Service (APHIS), the EPA, and the FDA. The 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). 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 products of biotechnology, pursuant to what legal authority, and when, in the commercialization process, regulatory oversight attaches, varies considerably.

The OSTP Memorandum

The July 2, 2015, the OSTP memorandum reflects the Administration's acknowledgement that the Coordinated Framework needs to be updated to capture and promote the tremendous explosion of new biotechnologies addressed by the federal family or regulatory agencies, as well as the lack, in some instances, of a coherent regulatory framework that innovators and others can anticipate and follow in commercializing their products (Holdren et al., 2015a). The OSTP memorandum directs the EPA, the FDA, and the USDA to initiate a process to update and modernize the Coordinated

Framework. A July 2, 2015, OSTP blog item entitled, "Improving Transparency and Ensuring Continued Safety in Biotechnology," (Holdren, Shelanski, Vetter, & Goldfuss, 2015b) notes that the complexity of the array of regulations and guidance documents developed by the EPA, the FDA, and the 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." (Holdren et al., 2015b, page 2).

> The memorandum states that the objectives:
> [A]re 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. (Holdren et al., 2015a, page 1).

The memorandum states that federal agencies regulating biotechnology products "should continually strive to improve predictability, increase efficiency, and reduce uncertainty in their regulatory processes and requirements." (Holdren et al., 2015a, page 4). 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

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- Promote public confidence in the oversight of the products of biotechnology through clear and transparent public engagement. (Holdren et al., 2015a, page 3).

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." (Holdren et al., 2015a. page 3).

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, the EPA, the FDA, and the USDA.

- ***Mission and Function of the Biotechnology Working Group***: Within one year of the date of the memorandum, the Biotechnology Working Group shall take the 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;" (Holdren et al., 2015a. page 3), 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…." (Holdren et al., 2015a. page 4).

- ***Independent Assessment***: The EPA, the FDA, and the USDA shall commission "an external, independent analysis of the future landscape of biotechnology products that will identify:
    1. potential new risks and frameworks for risk assessment, and
    2. areas in which the risks or lack of risks relating to the products of biotechnology are well understood." (Holdren et al., 2015a. page 5).

"This 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 five years." (Holdren et al., 2015a. page 5).

- ***Budgeting for Efficiency***: The EPA, the FDA, and the 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." (Holdren et al., 2015a. page 5).

- ***Annual Reporting***: For at least five years, starting one year after the release of the strategy described above, the Biotechnology Working Group "will produce an annual report on specific steps that agencies are taking to implement that strategy and any other steps that the agencies are taking to improve the transparency, coordination, predictability, and efficiency of the regulation of biotechnology products. This report will be made available to the public by the Executive Office of the President." (Holdren et al., 2015a. page 5).

The OSTP blog item issued on July 2 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, D.C., 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 form (Holdren et al., 2015b).

More recently, On October 16, 2015, the FDA, along with the OSTP, EPA, and the USDA announced in the Federal Register a public meeting to discuss clarifying the roles of various federal agencies in regulation products of biotechnology (FDA, 2015). The meeting is intended to discuss the FDA's role in responding to the July 2015 Executive Office of the President (EOP)

memorandum "Modernizing the Regulatory System for Biotechnology Products" and will invite oral comments from interested parties. The meeting will be held on October 30, 2015, at the FDA's offices in Maryland.

EPA Biotechnology Initiatives

Background of TSCA Regulation of Biotechnology

Several weeks after the White House issued the OSTP memorandum, EPA's OPPT announced that it is developing a project intended to support public dialogue concerning the development and use of biotechnology in industrial applications pursuant to its TSCA authority.

EPA's TSCA implementing regulations require manufacturers of "new" intergeneric microorganisms for commercial purposes to submit a notification to the EPA or otherwise to meet any of several available exemption procedures. In its biotechnology regulations, EPA states that "new" microorganisms are those that are intergeneric and not already listed on the TSCA Inventory (EPA, 2015b). An "intergeneric microorganism" is a microorganism formed by the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera. An "intergeneric microorganism" includes a microorganism that contains a mobile genetic element that was first identified in a microorganism in a genus different from the recipient microorganism (EPA, 2015b). EPA states that "[m]icroorganisms that are not intergeneric are automatically included on the Inventory" (EPA, 2015b), because conceptually, they are existing chemical substances. 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.

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's regulations provide that a notification exemption application will not be granted unless EPA can determine that the microorganism "will not present an unreasonable risk of injury to health or the environment." (EPA, 2015b).

Addressing Concerns Regarding Research and Development

In the preamble to the final microorganism regulations, EPA expressed its concern with R&D activities with microorganisms because EPA believes that living microorganisms, unlike traditional chemical substances, may "reproduce and increase beyond the number initially introduced, may establish in the environment, and may spread beyond the test site." (EPA, 1997a, p. 17923) Consequently, EPA provided two types of R&D exemptions for microorganisms in the final regulations. 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." (EPA, 1997a. p. 17933). 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," (EPA, 1997a. p. 17934) 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." (EPA, 1997a. p. 17948)

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. Health and safety data relating to a new microorganism's health or environmental effects that are in the submitter's possession or control must also be submitted to EPA with the TERA. The submitter must provide this information to the extent it is "known to or reasonably ascertainable by the submitter." (EPA, 1997a. p. 17949) 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, 1997a. p. 17949) EPA will so notify the submitter and the submitter can then proceed with the proposed activity as specified in the TERA. (EPA, 1997a. p. 17950). If, however, EPA concludes that it cannot determine that the R&D activity will not present such risks, the EPA will deny the TERA and provide reasons for its denial in writing.

Commercial Activities

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

Following a 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.

Exemptions from Commercialization Notifications

EPA has established a two-tiered exemption from notification requirements for commercialization of microorganisms that meet specified criteria. To qualify for the Tier I exemption:

- The microorganism must be one of ten species specified in the regulations;

- The microorganism must meet introduced genetic material criteria (*i.e.*, limited in size, well-characterized, poorly mobilizable, and free of certain toxin-encoding sequences);
- The physical containment and control technologies of any facility in which the microorganism will be manufactured, processed, or used must meet certain criteria; the manufacturer or importer submits a certification at least ten days prior to commencing initial manufacture or import of the new microorganism; and
- The manufacturer or importer complies with recordkeeping requirements.

The Tier II exemption provides for an expedited review of microorganisms that satisfy Tier I requirements, except for the requirement that the facility meets all necessary physical containment and control technologies requirements. 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. EPA will approve or deny the Tier II exemption request no later than 45 days after the agency receives the request.

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). 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." (EPA, 1997b.) EPA will either approve or deny a TME application no later than 45 days after receipt, and may impose restrictions with approval. The submitter "may only proceed with test marketing activities after receipt of EPA approval." (EPA, 1997a. P. 17951).

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EPA Guidance Documents

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 MCANs or TSCA TERAs for various commercial products. The Points to Consider document helps submitters identify and organize the information and data they provide to inform the EPA's required risk assessments. An important component of EPA's recent announcement is the statement 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." (EPA, 2015a). 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" (EPA, 2015a) 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. This is important, as the OPPT notes that there has been a significant jump in MCAN submissions, and some include algae cases, which the OPPT expects will increase as the technology ramps up.

EPA's recently posted document states that it is focusing its project around biotechnology algae applications. In light of the uptick in the number of TSCA MCAN submissions, EPA wishes to develop guidance to assist innovators in evaluating potential risks posed by such technologies. The algae document will evolve as a separate, stand-alone document so that EPA

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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 algal and genetic engineering technologies simultaneously can be highlighted in a way that the current *Points to Consider* cannot readily do." (EPA, 2015a). 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 biology. 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, 2015a).

Facilitating Public Engagement

EPA intends to facilitate such engagement by convening an expert workshop, open to the public, on September 30, 2015. While the expert workshop reportedly will focus on the technical questions that EPA believes are important to its development of a biotechnology algae considerations document, EPA states that it will also provide an opportunity for stakeholders and the general public to comment on any aspects of biotechnology algae they believe are relevant to the EPA's mission.

Following the expert workshop, EPA will consider 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 the EPA's premanufacture review authority under TSCA. EPA also expects that public awareness of its biotechnology algae document will lead to broader questions about the introduction of products of biotechnology into commerce.

EPA states that it recognizes the potential of biotechnology to create new benefits for society, and, therefore, supports its development in the United States. 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, 2015a).

EPA states 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, 2015a). 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." (EPA, 2015a).

Discussion

Modernizing seems to be the word *de jure.* For years now, efforts have been underway to modernize TSCA, and as we speak, there is reason to believe TSCA reform legislation may be enacted later this year. Despite the significant role TSCA plays in the United States regulatory system for products of biotechnology, curiously, there has been virtually no discussion

of or attention given to TSCA's application to products of biotechnology in the TSCA reform debate. That the modernizing of the Coordinated Framework will occur on a separate trajectory, perhaps in parallel with implementing TSCA reform legislation—should it happen this year—poses both risks and opportunities.

That the Coordinated Framework needs a "do over" is clear. 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 the Administration announced on July 2. In 2014, the J. Craig Venter Institute issued its *Synthetic Biology and the U.S. Biotechnology Regulatory System, Challenges and Options*[ii] Report's landmark analysis of the domestic biotechnology regulatory system in which it highlighted the critical need for modernizing the Coordinated Framework.[iii] 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.[iv]

The Administration's decision to modernize the Coordinated Framework is welcome news. If TSCA reform legislation is enacted, 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, it will be interesting to see how the two initiatives progress in tandem. The OPPT's regulatory initiatives are equally important, as the need for guidance on the development of biotechnology algae will greatly assist innovators in commercializing their products.

Similarly, the need for public debate on biotechnology in general is critical. In updating the Points to Consider document, developing a stand-alone biotechnology algae document, and encouraging public discourse on pertinent industrial biotechnology applications, the public will be afforded an opportunity to participate in the process and understand better how these technologies are regulated. This will, in turn, help assure greater confidence in EPA's ability to explain its oversight of these products, and help stakeholders appreciate the promise that these products offer to society.

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End Notes

[i] 51 Fed. Reg. 23302 (June 26, 1986); 57 Fed. Reg. 6753 (Feb. 27, 1992).

[ii] http://www.jcvi.org/cms/research/projects/synthetic-biology-and-the-us-biotechnology-regulatory-system/overview/.

[iii] J. Craig Venter Institute. *Synthetic Biology and the U.S. Biotechnology Regulatory System: Challenges and Options* (May 2014), available at www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-biology-and-the-us-regulatory-system/full-report.pdf.

[iv] *See* http://www.nap.edu/catalog/19001/industrialization-of-biology-a-roadmap-to-accelerate-the-advanced-manufacturing.