EPA Oversight of Synthetic Biology

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EPA Has Regulatory Authority Over Synthetic Biology Products Under The Toxic Substances Control Act

- Synthetic Biology is regarded as a form of Biotechnology
- EPA has used TSCA for oversight of new biotechnology since 1986 with formal regulations issued in 1997*
- Synthetic Biology products were included in the EPA Coordinated Framework component that established TSCA authority over some biotechnology products

*Microbial Products of Biotechnology; Final Regulation Under the Toxic Substances Control Act

Toxic Substances Control Act (TSCA) and Genetically Engineered Microorganisms

- **TSCA Authority**
  - Under TSCA, EPA has the authority to regulate the manufacture, use, distribution in commerce, and disposal of “chemical substances and mixtures.”
  - Through the Coordinated Framework* policy statement and 1997 Rule, certain microorganisms, were included as substances within this authority
  - TSCA requires premanufacturing notification of all 'new' substances not otherwise excluded or exempted
- **TSCA covers chemical substances (typically used in environmental, industrial, or consumer products) that are not specifically excluded**
  - Substances Specifically Excluded from TSCA Regulation
    - Pesticides, but not pesticide intermediates (EPA/OPP FIFRA)
    - Food, food additives, drugs, cosmetics, and their intermediates, and substances used as medical devices
    - Tobacco and tobacco products
    - Nuclear materials

- *Coordinated Framework for Regulation of Biotechnology (OSTP, June 26,1986)

“New” Microorganisms Subject to TSCA

- **“New” microorganisms are :**
  - **those formed by deliberate combinations of genetic material from organisms classified in different taxonomic genera (intergeneric)**
  - **constructed with synthetic genes that are not identical to DNA that would be derived from the same genus as the recipient cell**
  - **are not listed on TSCA Inventory**
  - **used in TSCA applications**
- **Exclusions**
  - **naturally occurring microorganisms**
  - **genetically engineered microorganisms other than intergeneric**
  - **intergeneric microorganisms resulting only from the addition of well-characterized, non-coding regulatory regions**

Coordinated Framework Use of 'Chemically Synthesized'

- Unit III.C. *Specific Requirements Under TSCA*

  1. *Premanufacture notification requirements—a. Overview.*

  – "Organisms are considered dissimilar for the purposes of this policy if they are from different genera. In the case of chemically synthesized genes, the Agency will follow the same principle, as clarified below in Unit IV."

- Unit IV. Definitions of Terms for Regulatory Purposes

  A. How To Determine if a Product Is an Inter-Generic Combination

  – "In the case of chemically synthesized genes, the Agency will follow 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 will be considered intrageneric"…. (otherwise the resulting microorganism will be considered intergeneric)

1997 TSCA Biotech Rule

- **Rule established mechanisms for reporting to EPA, including a number of specific exemptions**
  - **MCAN - Any manufacturer, importer, or processor must file a Microbial Commercial Activity Notice (MCAN) 90 days prior to initiating manufacture/import (unless the activity is eligible for an exemption)**
  - **TERA - Persons who wish to introduce a new microorganism into the environment for commercial R&D purposes must submit a TSCA Experimental Release Application (TERA) (similar to an abbreviated MCAN submission) 60 days prior to initiation of the field test**
  - **Tier I and Tier II Exemptions - Exemptions from MCAN filing are available for closed system commercial activities utilizing approved recipient organisms (40 CFR 725.420), meeting certain criteria for the introduced genetic material, and specific containment/control technologies**

Possible Regulatory Decisions

- **Sufficient information to determine "no unreasonable risk"**
  - no regulatory action taken
  - company may commence manufacture after the 90 days
  - once manufacture begins and EPA receives Notice of Commencement, organism is listed on the TSCA Inventory
- **Sufficient information to determine "unreasonable risk"**
  - Section 5(f) or 6(a) – prohibit or restrict use
- **Insufficient information to determine effects, but possibility exists for unreasonable risk and/or substantial/significant exposure**
  - Section 5(e) – negotiate Consent Order to restrict use & specify data needs to lift Consent Order

Data Needs for MCANs or TERAs

"Points to Consider" Guidance Document Elements

- **taxonomic descriptions of the recipient and donor microorganisms**
- **detailed construction of the submission microorganism**
- **human health effects information on the submission microorganism**
- **environmental effects information on submission microorganism**
- **by-products, production volume, and use information**
- **worker exposure and environmental releases/containment /mitigation**
- **environmental release protocols**
- **expected survival/dispersal - environmental exposures**
- **emergency/contingency protocols**

Issues for Synthetic Biology

All Synthetic Biology is Equal But Some Synthetic Biology is More Equal Than Others[1]

[1] Apologies to George Orwell

Techniques with which EPA has had Experience

- **Single Gene Modification**
  - Chemically synthesize sequence to alter codon utilization to fit preference of recipient microorganism
  - Can include resynthesis of native gene to fit majority codon usage
- **Enhanced Metabolic Engineering (ME)**
  - Replace entire, or parts of, desired pathways
    - Multiple genes
    - Synthetic sequences
  - Most ME tends to be intergeneric and thus 'new'. Some ME may use only pathway components from within the recipient genus --- thus not new.
- **EPA would interpret these as subject to oversight**
- **EPA has seen lots of this 'synthetic biology'**

Techniques with which EPA has not had experience

- **Orthogonal life**
  - xeno-nucleic acids (XNA)
  - Orthogonal protein translation
    - Synthetic codons
    - Synthetic tRNAs
    - Synthetic ribosomes
  - Synbio by any definition

- **Minimal Genomes and Synthetic Genomes**
- Multiplex Automated Genome Engineering/Conjugative Assembly Genome Engineering. (MAGE/CAGE)
- Chemically synthetic genomes
  - The *Mycoplasma mycoides* experiment
    - But is it new?
  - Reengineering whole genomes
    - Using orthogonality


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Most Difficult to Assess

- Orthogonal Life – No previous experience / no analogs
- Wholesale ME that adds complete pathways that were not well studied in the native organism
- Modification of pathways that are not well understood in the recipient organism

Office of Pollution Prevention and Toxics

Items available at:

http://www.epa.gov/oppt/biotech

Microbial Products of Biotechnology; Final Regulation Under the Toxic Substances Control Act; Final Rule -40 CFR Parts 700, 720, 721, 723, and 725

Points to Consider in the Preparation of TSCA Biotechnology Submissions for Microorganisms

Coordinated Framework for Regulation of Biotechnology; Announcement of Policy and Notice for Public Comment

Thank You!

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