



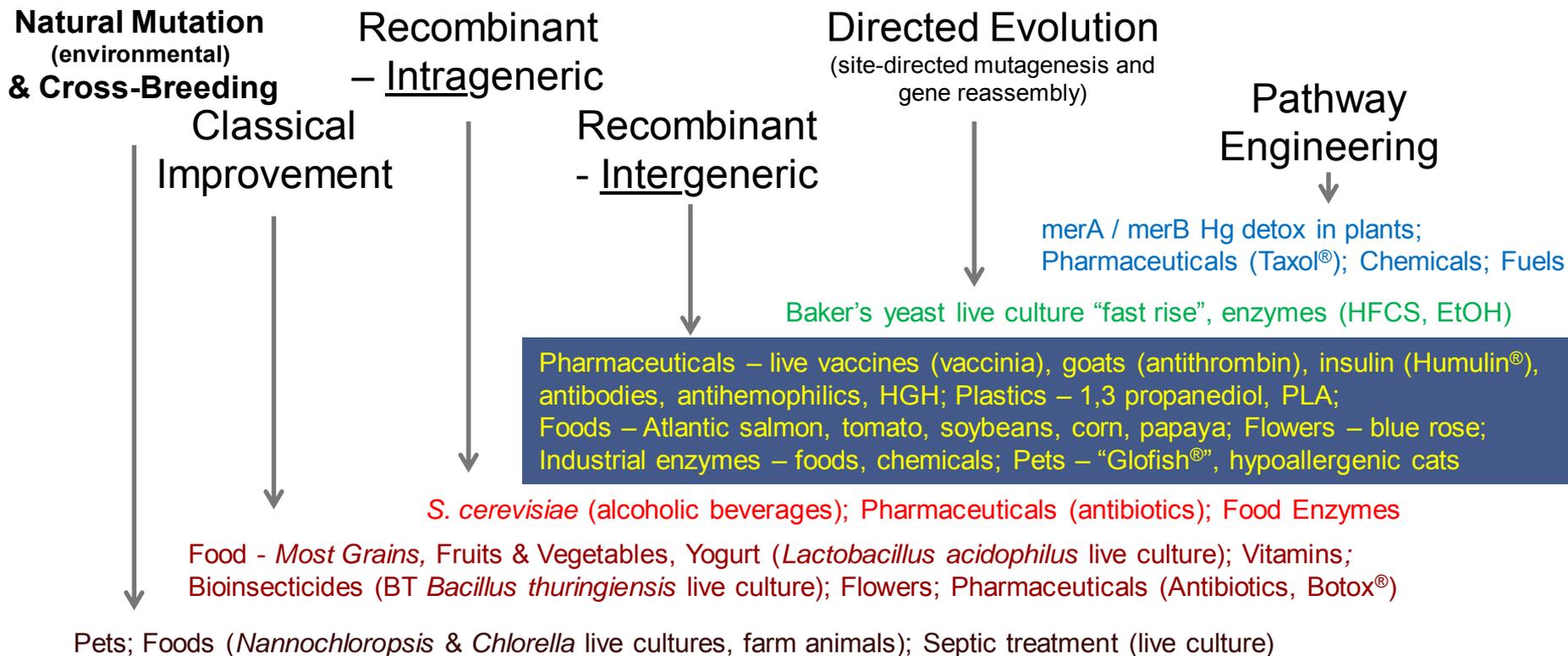
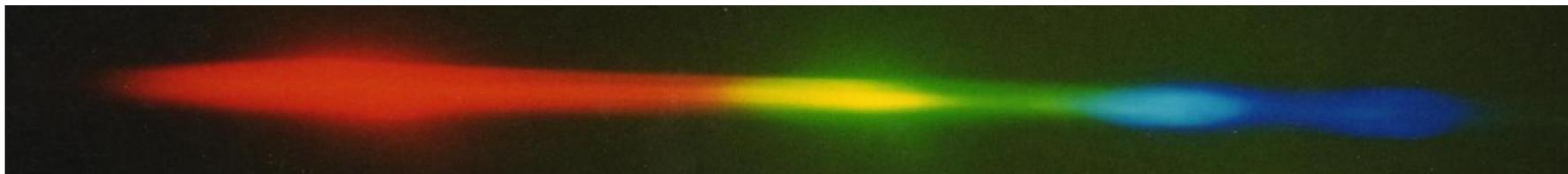
SYNTHETIC GENOMICS®

Federal oversight for natural and engineered microalgae

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US DOE Biomass Conference July 10, 2012

Federally-Regulated Products Across the Continuum of Genetic Modification



US Coordinated Framework: Regulation of Biotechnology

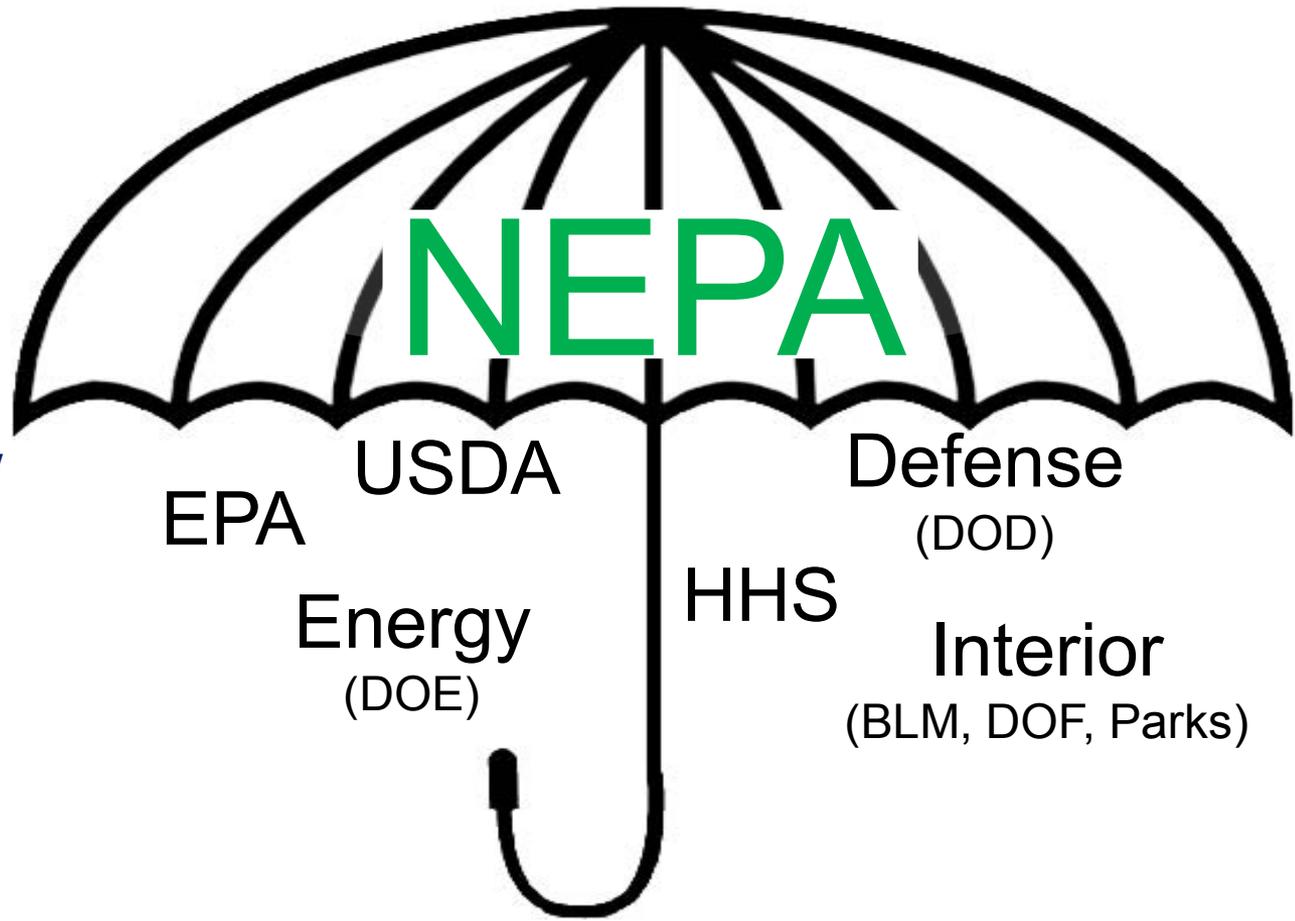
- Lead Federal Agencies:
 - Environmental Protection Agency (**EPA**)
 - Toxic Substances Control Act (TSCA)
 - Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
 - Department of Agriculture (**USDA**)
 - Plant Protection Act (PPA)
 - Department of Health and Human Services (**HHS**)
 - National Institutes of Health (NIH) Guidelines oversee federally-funded research
 - Food and Drug Administration (FDA)
 - Federal Food, Drug and Cosmetic Act (FFD&C Act)
 - Public Health Service Act
- Agencies with Secondary Roles:
 - Centers for Disease Control (CDC) - refer to BMBL Rev. 5
 - Department of Labor (OSHA)
 - State Governments
- National Environmental Policy Act (NEPA)



National Environmental Protection Act

- **NEPA: All “major federal actions” must have an Environmental Impact Statement (EIS) and examine the consequences before proceeding.**
- **Pursues a balance of social, environmental and economic factors.**
- **EPA has a unique responsibility to review and comment on other agencies’ EIS. And, as a consequence of its mission, EPA’s review can be functionally equivalent to an EIS. See e.g., *Portland Cement Ass’n v. Ruckelshaus*, 486 F.2d 375, 384-85 (D.C. Cir. 1973).**

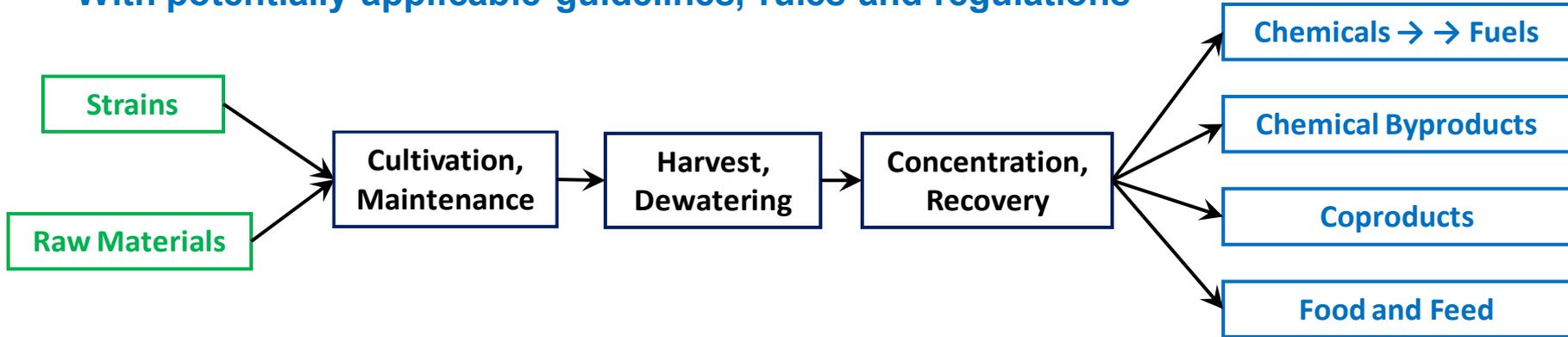
42 U.S.C. 4321 *et seq.*; 40 C.F.R. 1500 – 1508



SYNTHETIC GENOMICS®

Simplified Microalgae/Cyanobacteria Regulatory Road Map

With potentially-applicable guidelines, rules and regulations



| | Strains / Raw Materials | Manufacturing Process | Products |
|------------|--|---|--|
| R&D | <ul style="list-style-type: none"> NIH - rDNA Guidelines, Screening Framework of DS rDNA EPA TSCA - TERA, R&D contained-use exemption USDA -GMO importation , interstate movement and open system research with known plant pests State biotechnology and/or aquaculture regulations | <ul style="list-style-type: none"> OSHA – General duty clause EPA TSCA – TERA, R&D contained use exemption USDA - plant pests in open and closed systems State biotechnology and/or aquaculture regulations Local Zoning | Federal, state and/or local permits (air, water intake, air emissions, wastewater, storm water discharge, RCRA, OSHA, building and fire codes etc.) may be applicable to certain R&D activities. |
| Commercial | <p>Inputs such as strains, chemical substance feedstocks, processing aids, nutrients, CO₂, and water regulated by EPA, FDA and other federal, state, local agencies</p> <p>Air and water emissions, wastes are regulated by EPA and other federal, state, local agencies</p> | <ul style="list-style-type: none"> OSHA – General duty clause and others EPA TSCA – MCAN EPA FIFRA – pest management USDA – plant pests used in open systems FDA – for FDA-regulated products TTB – for ethanol, butanol production NEPA, ESA may apply if federal funding State biotechnology and/or aquaculture regulations; Local zoning | <p><u>Product-Specific Regulation</u></p> <ul style="list-style-type: none"> Chemicals - EPA - TSCA PMN Fuel - EPA /DOD/DOT/FAA – fuel certification Fuel - EPA - RFS compliance Ethanol, Butanol - TTB Food – FDA CFSAN Feed – FDA CVM / AAFCO Plus items listed above for R&D |

US Department of Agriculture – APHIS

A genetically modified algae cultivated outdoors falls within USDA's statutory authority under the Plant Protection Act – if it is a ***plant pest***



- “Eukaryotic algae” are included in the regulatory definition of “plant”
- The definition of *regulated plant* under 7 C.F.R. 319.37-1 is proposed to include “nonvascular plants include mosses, liverworts, hornworts, and green algae.” 74 Fed. Reg. 36403 (July 23, 2009)
 - not limited to green algae (red, brown are nonvascular plants by extension)
- Under current and proposed 2008 rules microalgae are not plant pests
- USDA does not approve field trials of microalgae at this point in time.
- USDA is ***proposing*** phytosanitary permits 30 days before import of micro-algae (natural and modified).



US Environmental Protection Agency - OPPT

- EPA regulates new microbial products of biotechnology under the Toxic Substances Control Act (TSCA)
- TSCA can require obligations regarding reporting, management, storage, containment, use and disposal
- Reporting required for “new” microorganisms
 - Requirements can be extensive and lead to further regulation
- Some precedent for small scale releases of modified organisms for limited durations



Microbes Are Chemical Substances

- TSCA regulates “chemical substances”:
 - [a]ny organic or inorganic substance of a particular molecular identity, including -- (i) any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature...
 - [includes microorganisms](#)
- Foods and pesticides are excluded from the above definition
 - All food precursors and intermediates are treated as food and are also excluded (except when the EPA wants to assert jurisdiction).
 - Pesticide precursors are covered by TSCA unless they also happen to be a registered pesticide (FIFRA).



Microbes Are Already On the TSCA Inventory *if*:

- They are **naturally occurring** (not more than minimally processed);
 - classically improved through mutagenesis included here
- Contain introduced genetic material consisting of only well-characterized, **non-coding** regulatory regions from another genus
- Are manufactured, imported, or processed **solely for academic research**, or solely for export
- Are **mixtures** of micro-organisms (individual constituents may be reportable)

Remember:

- TSCA doesn't cover food / feed applications – work with FDA
- TSCA doesn't cover pesticides – work with EPA under FIFRA



Fuel Production is a TSCA Use

- EPA regulates a “new”, intergeneric microbe that is manufactured, imported, or processed for a commercial purpose that is regulated by TSCA
 - Industrial fuel production = regulated by TSCA
- Manufacture, process, use in R&D designed to obtain an immediate or eventual commercial advantage = commercial purpose. *40 C.F.R. 720.3(r)*

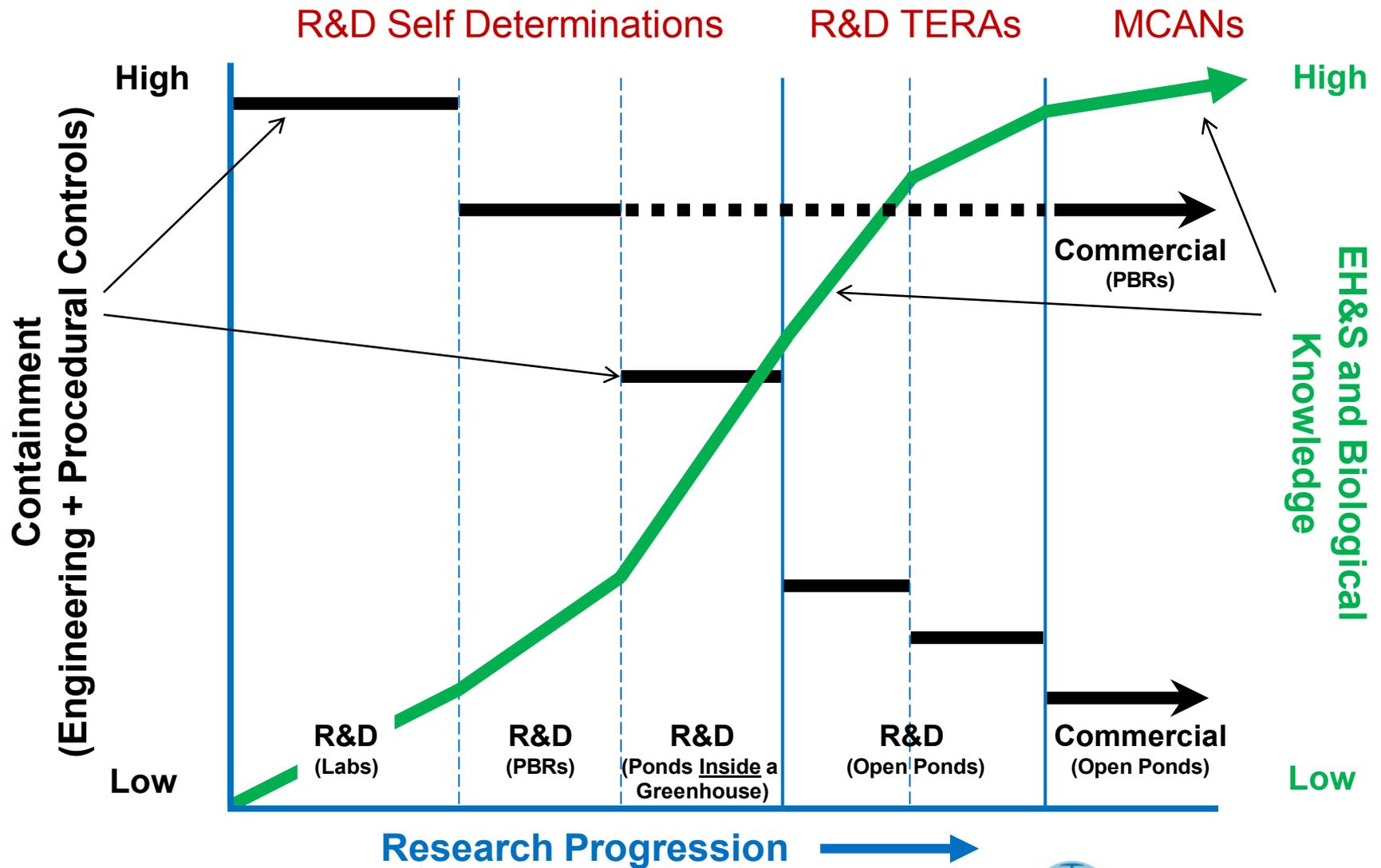


What should I file? MCAN, TERA or TME?

- **MCAN** (Microbial Commercial Activity Notification)
 - Must submit **notification** to EPA AT LEAST 90 days before *non-exempt manufacture* or import of a new intergeneric microbe.
 - Substantial data requirements.
- **TME** (Test Marketing Exemption)
 - Fixed exemption duration. Must define TM activity and how it may be distinguished from full scale commercial production and R&D activities.
 - Must submit to EPA AT LEAST 45 days before activity is **approved**.
 - All available data concerning actual or potential effects on health or the environment.
- **TERA** (TSCA Experimental Release Application)
 - R&D programs are strongly encouraged by EPA to pursue a TERA before filing an MCAN.
 - May be applied to outdoor raceway pond concepts at small and medium scale testing facilities.
 - Must submit to EPA AT LEAST 60 days before activity is **approved**.
 - Substantial data requirements.



GM Microorganism Containment is a Function of EH&S and Biological Knowledge



R&D Conducted Inside a Structure

- R&D contained “inside a structure” equals self determination of compliance
- May be applied to both greenhouses and photobioreactors



Self-Determination R&D Conducted Inside a Structure

- Eligibility Requirements per 40 C.F.R. 725.234
 - Manufactured, imported, or processed microorganism solely for R&D activities;
 - Supervised by a technically qualified individual (TQI);
 - No intentional testing outside of a structure;
 - Use of containment and/or inactivation controls;
 - Selected by the TQI and approved and certified by another authorized individual
 - Designed to *restrict* release of the R&D organism
 - Record controls utilized; and
 - Notify employees and recipients of risks.
- Associated risk assessment, risk communication, and recordkeeping requirements per 40 C.F.R. 725.235

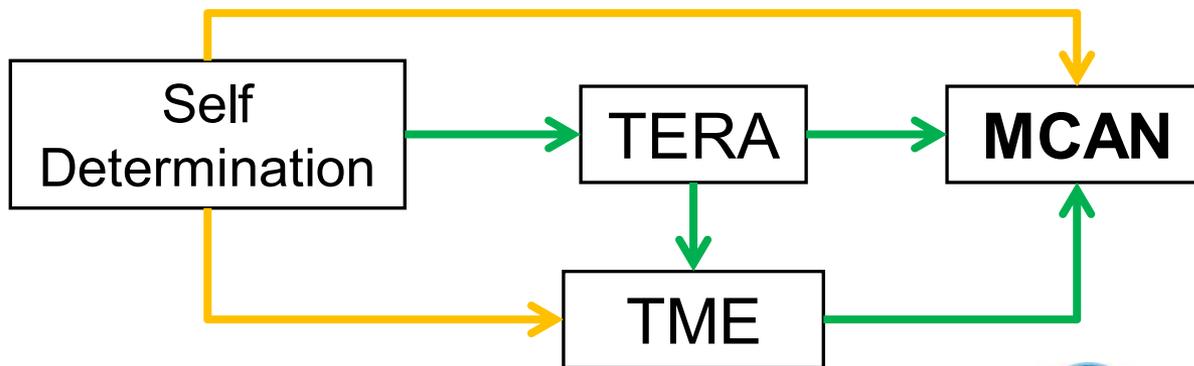


TERA (TSCA Experimental Release Permit) R&D Conducted Outside a Structure

- Notification required for R&D testing of new microorganisms that are released into environment
 - Designed for use in field trials
 - Designed for R&D activities funded by a commercial entity or which will obtain an immediate or eventual commercial advantage for the researcher
 - Akin to an abbreviated MCAN
- A person may submit a TERA for one or more microorganisms and one or more research and development activities, including a research program.
725.250(c)
- Submit to EPA *at least* 60 days prior to initiating contemplated field trials
 - Shorter review period (theoretically)
 - Provides more flexibility than an MCAN



MCAN (Microbial Commercial Activity Notification) Non-R&D Activity Conducted Outside a Structure



Naturally Occurring vs. Intergeneric Microalgae Regulation

Naturally Occurring

- **MOVEMENT:** No USDA APHIS interstate movement permit is needed for transport within the US, unless it is regulated as a plant pest.
- **CONTAINED USE:** No USDA or EPA notification needed for R&D or commercial production.
- **PHOTOBIOREACTORS:** No USDA or EPA notification needed.
- **PONDS:** No USDA or EPA notification needed.
- **STATES:** Import permit might be needed for non-native species, and possibly an aquaculture permit.
- **OTHER:** Subject to USDA if ruled a plant pest.

Intergeneric

- **MOVEMENT:** No USDA APHIS interstate movement permit is needed for transport within the US, unless it is regulated as a plant pest. No USDA phytosanitary permit needed for import. Either could change.
- **CONTAINED USE:** No USDA or EPA notification needed for R&D. MCAN for commercial production.
- **PHOTOBIOREACTORS:** No USDA or EPA notification needed if deemed contained for R&D. MCAN for commercial production.
- **PONDS:** Notification to EPA needed via a TERA for R&D. MCAN for commercial production.
- **STATES:** Import permit might be needed for non-native species, and possibly an aquaculture permit.
- **OTHER:** No USDA environmental impact assessment required for field release unless a plant pest already or plant pest coding added. This could change.

