Government Regulation of Synthetic Biology: Is the existing framework sufficient to address use of SynBio in industrial biotechnology?

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“Synthetic biological creations are designed to self-replicate and once released into the environment they would be impossible to stop. The ways in which these organisms will interact with the natural environment is unpredictable, potentially devastating, and permanent”.  

“Synthetic biologists are capable of designing organisms with no relatives in nature”. 

The technical ability ... to create synthetic organisms far outpaces our understanding of how these novel products may work. Even engineering supposedly simple organisms could have major ecological and health effects”.  

1. Synthetic Biology 101, Friends of the Earth 2013  
2. David Wei, FIELD, undated.  
3. Principles for the Oversight of Synthetic Biology, FOE, CTA, ETC, 2012
“The underlying principles for synthetic biology are the **same as those for more traditional rDNA techniques**: the biggest differences are size, scope, accuracy and speed of genetic changes ... Even [in early demonstrations], **re-design of the genome has been modest**”.¹

“The first generation of synthetic biology products is, or may likely be, relatively simple and **similar to other genetically engineered products**, [and] in the short term ... are **unlikely to raise novel risk assessment or risk management issues**”.², ³

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¹ J. Craig Venter Institute, 2014
² “New Life, Old Bottles”, 2009
³ Presidential Commission, 2010
U.S. Regulation of Synthetic Biology Research

* **NIH Guidelines**: recently amended to explicitly cover synthetic DNA molecules.

* **Select Agents**: USDA, CDC regulations that restrict possession, use, importation and transfer of select agents and toxins now prohibit or require permits for some uses of synthetic nucleic acids encoding toxins.

* **Screening Framework Guidance** to monitor export of synthetic double-stranded DNA.

* **Outdoor R&D**: oversight required under all biotech regulation (NIH Guidelines, EPA, USDA rules).
Environmental Protection Agency

* Microbial pesticides, plant pesticides.
* Engineered microorganisms used for other industrial purposes.

U.S. Department of Agriculture

* Transgenic plants, potential plant pests.
* Plant-produced industrial products.

Food and Drug Administration

* Foods, food additives, pharmaceuticals.
EPA TSCA Biotechnology Regulations: Overview

- Regulations adopted in 1997 under the Toxic Substances Control Act (TSCA) cover commercial uses of new (“intergeneric”) microorganisms not regulated by other agencies: primary rules covering industrial biotechnology.

- **R&D:** No oversight for contained activities; advance EPA approval needed for outdoor research (TSCA Experimental Release Application; TERA).

- **Commercial Uses:** Advance EPA review needed for most commercial applications through filing of Microbial Commercial Activity Notice (MCAN). Exemptions require strict adherence to containment provisions.
EPA Regulation under TSCA: Applicability to SynBio

- **EPA policy**: if the sequence of a synthesized gene is different from, or not known to be identical to, a sequence in the genus of the recipient microorganism, the resulting product is considered intergeneric.
- Most microorganisms made via synthetic biology for a TSCA purpose would be covered.
- Even presence of a small number of synthetic or nonnative nucleotides or codons in a native gene would cause the organism to be considered intergeneric.
- Environmental use of new organisms always covered, both for R&D and commercial use.
Regulations issued in 1987, administered by USDA Animal and Plant Health Inspection Service (APHIS), cover environmental uses or interstate movement of organisms considered to be “potential plant pests”.

**R&D:** Rules generally cover only outdoor research, requiring either a permit or USDA advance notice; suitable confinement provisions must be in place.

**Commercial use:** Approval for commercial use and sale through “petitions for nonregulated status”, based on years of field testing and substantial data on environmental effects.
Potential plant pest status is usually based on presence of DNA sequences from listed genera and species.

But the definition of “regulated article”: Any organism which has been altered or produced through genetic engineering, if the donor organism, recipient organism, or vector or vector agent is an unclassified organism and/or an organism whose classification is unknown, or ... which the Administrator determines is a plant pest or has reason to believe is a plant pest.

APHIS recently announced its intent to revisit possible regulatory revisions to broaden applicability.
Under most national laws, especially where subject to Cartagena Protocol, any modified organism would be subject to regulation.

- **Living modified organism (LMO)** defined as “any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology “.

Even under the laws of nonconforming nations, organisms made by synthetic biology would be covered. For example:

- **Canada**: New Substance Regulations apply to any microorganism new to commerce in Canada.
- **Europe**: “organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination”.
- **Australia**: gene technology: “any technique for the modification of genes or other genetic material”.
March 2015 publication of two information documents submitted to the Conference of the Parties, to support work of Ad Hoc Technical Expert Group on Synthetic Biology.

Among its conclusions:

- Precautionary principle is relevant but its implications for SynBio are not clear.
- Living organisms resulting from current SynBio techniques are LMOs as defined by the CBD, and subject to its biosafety provisions and to the requirements of the Cartagena Protocol.
- Although there may be gaps for components and products that are not living organisms, overall, the components, organisms and products resulting from SynBio would fall under the scope of a number of regulatory mechanisms.
European Commission: 
**Opinion on SynBio Risk Assessment Methods**

Second of 3 opinions on SynBio to be issued by EC and its non-food Scientific Committees: June 16, 2015. Findings (emphasis added):

- The **current methodology used for GMO risk assessment can be extended to SynBio developments**, given similarities in methodologies and tools, but there are specific cases in which new approaches may be necessary.

- **Present risk assessment methodologies are appropriate** for assessing potential risks of SynBio activities and products. However, several improvements can be made to ensure continued safety protection proportionate to risk.

- Safety locks currently available in genetic engineering are not yet sufficiently reliable for SynBio.

- A clear strategy for developing new forms, additional layers, of bio-containment is needed.
The robust risk assessments needed for synthetic biology work for occupational health protection and to address public health concerns are at present covered by Genetically Modified Organisms regulations.

The general view is that the current risk analysis system for GMOs also applies to synthetic organisms, although difficulties could arise in assessing the characteristics of an organism that has been created via the bottom-up approach.

With proper regulation and risk assessments, the consensus is that the likelihood of an untoward incident involving accidental or deliberate release of a modified organism could be significantly reduced.
For the foreseeable future, “synthetic” organisms will all be based on a naturally occurring “host” species, so that risk assessments can use familiar principles.

- Does the organism have harmful or deleterious properties, e.g. toxicity, pathogenicity, enhanced competitiveness?
- If released to the environment, will the organism survive, multiply, compete and disseminate in the environment?
- Horizontal gene transfer: can genetic material be transferred to indigenous organisms?
- Will any of the above cause adverse ecological effects?
Containment Principles: Industrial Microorganisms

- Assign host organism to a “Risk Group”.
- Use well-established principles of Good Laboratory Practice, Good Large-Scale Practice, commensurate with Risk Group of the organism.
- Controlled access to facility.
- Inactivation of liquid and solid wastes.
- Minimize release from air vents, other potential release points.
- Institute spill control procedures and other emergency protocols.
Confinement Principles: Plants

- Follow established practices in transporting and planting transgenic plants and disposal of wastes.
- Locate field tests away from areas of commercial production.
- Include buffer zones in the test plots.
- Employ measures to prevent pollination.
- Air, soil and water monitoring as appropriate during field trials.
- Scouting for volunteers after trial has concluded.
Earliest commercial organisms will not be “entirely new life forms” – they will be modified with synthetic versions of a relatively small number of genes, enabling adequate risk assessment.

The principles of risk assessment are sufficient for commercial or large-scale uses.

Principles of containment/confine ment/monitoring sufficient for R&D uses.

Appropriate to continue to assess adequacy of regulations and risk assessment methodology.
Although it is legitimate to review the adequacy of regulations, many of the critics are recycling arguments and scare tactics from the 1970s and 1980s.

Consensus of most governments and international bodies is that current regulations and risk assessment methods are sufficient for organisms likely to be created in the short term.

General acknowledgement that more advanced products of synthetic biology may require additional levels of scrutiny.
Thank you very much

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