

Future Products of Biotechnology and Needs for Risk Analysis Science

Findings and Recommendations of 2017 National Academies report
Preparing for Future Products of Biotechnology

2018 AAAS Annual Meeting, Austin, February 18, 2018

Moderator: Kara Laney, National Academies of Sciences, Engineering, Medicine

Presenters: Richard Murray, California Institute of Technology, Committee Chair
Mary Maxon, Lawrence Berkeley National Laboratory, Committee Member
Steve Bradbury, Iowa State University, Committee Member

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#BiotechStudy

The National Academies of Sciences, Engineering, and Medicine

- Advisors to the Nation on science, engineering, and medicine.
- National Academy of Sciences created in 1863 under Lincoln Administration. National Academy of Engineering and National Academy of Medicine established in the 20th century.

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Committee on Future Biotechnology Products

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Institute of Technology

Martha Krebs, Pennsylvania State
University

Raul F. Medina, Texas A&M University

Steven P. Bradbury, Iowa State University

Barbara J. Evans, University of Houston
Law Center

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Richard Amasino, University of Wisconsin,
Madison

Jennifer Kuzma, North Carolina State
University

Jeffrey Wolt, Iowa State University

David Rejeski, Woodrow Wilson Center for
International Scholars

Farren Isaacs, Yale University

**Biotechnology (academic and
industrial)**

**Biotechnology Law, Regulation, and
Policy**

Energy Science and Policy

Entomology and Evolutionary Ecology

Environmental Toxicology

Genetics and Genomics

Microbial Physiology and Biochemistry

**Molecular Biology and Synthetic
Biology**

Plant Biochemistry and Genomics

Risk Analysis and Governance

Impetus for the Study

July `15

Apr `16

July `16

Oct `16

Jan `17

Mar `17

2015 White House Memorandum calling for modernization of the biotechnology regulatory system:

- Update the Coordinated Framework
 - Clarify the roles and responsibilities of the agencies that regulate to “products of biotechnology”
- Formulate long-term strategy for biotechnology regulatory system
 - Efficiently assess risks associated with future products of biotechnology
 - Support innovation, protect health and environment, promote public confidence in regulatory process, increase transparency and predictability, reduce unnecessary costs and burdens
- Commission an external, independent analysis of the future landscape of biotechnology products

Statement of Task

What will the likely future products of biotechnology be over the next 5-10 years? What scientific capabilities, tools, and/or expertise may be needed by the regulatory agencies to ensure they make efficient and sound evaluations of the likely future products of biotechnology?

- (1) Describe the major advances and the potential new types of biotechnology products likely to emerge over the next 5-10 years.
 - (2) Describe the existing risk analysis system for biotechnology products ... and each agency's authorities as they pertain to the products of biotechnology
 - (3) Determine whether potential future products could pose different types of risks relative to existing products and organisms. Where appropriate, identify areas in which the risks or lack of risks are well understood.
 - (4) Indicate what scientific capabilities, tools, and expertise may be useful to support oversight of potential future products of biotechnology
- (Human drugs and medical devices are not in the purview of the study.)

Study Relevant Activities

July `15

Apr `16

July `16

Oct `16

Jan `17

Mar `17

Committee activities

- April 18-19: Meeting 1 (2 days; DC)
- June 1-3: Meeting 2 (3 days; DC)
- June 27-28: Meeting 3 (2 days; SF)
- July: 8 Webinars
- August 1-5: Writing Meeting (5 days; Irvine)
- Oct-Nov: Report review
- Dec-Jan: Report revision in response to review
- Feb-Mar: Final approval and release of report

Information gathering

- 74 speakers (acad, industry, NGO)
- 180 papers, books and reports
- Public sessions, comments (100+)
- 17 federal offices; public databases

Report review

- 17 external experts
- Response to all comments
- Report review committee

US Government activities

- July 2015: Establishment of Biotechnology Working Group (BWG)
- June 2016: Passage of New TSCA (Toxic Substances Control Act)
- Sep 2016: Updated Coordinated Framework (draft) + National Strategy
- Jan 2017: Release of final updated Coordinated Framework

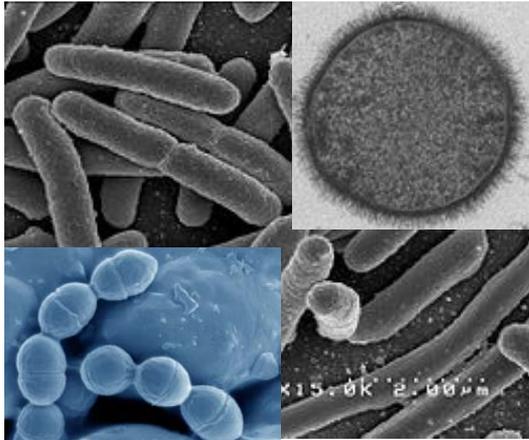
Outline of the Report

1. Introduction and Context
2. Emerging Trends and Products of Biotechnology
 - Setting the Stage: Understanding the Key Drivers for Future Biotechnology Products
 - Future Biotechnology Products
3. The Current Biotechnology Regulatory System
 - Overview of U.S. Regulatory System
 - Consumer and Occupational Safety
 - Environmental Protection
4. Understanding Risk Related to Future Biotechnology Products
 - Risks from Future Biotechnology Products: Similarities to the Past and Gaps Going Forward
 - Existing Federal Capabilities, Expertise, and Capacity
5. Opportunities to Enhance the Capabilities of the Biotechnology Regulatory System
 - Consistent, Efficient, and Effective Decision Making for Future Products of Biotechnology
 - Technical Toolbox and Capabilities for Risk Assessment and Regulatory Science
6. Conclusions and Recommendations

Cross-Cutting Themes

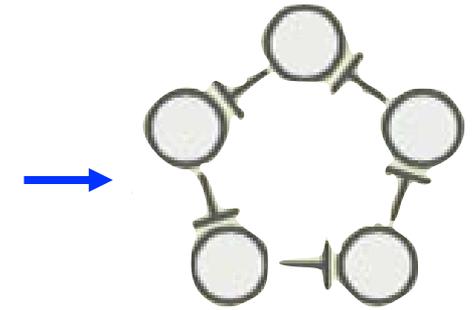
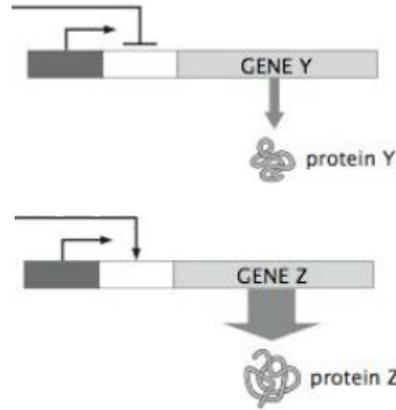
- The bioeconomy is growing rapidly and the U.S. regulatory system needs to provide a *balanced approach* for consideration of the many competing interests in the face of this expansion
- The *profusion* of biotechnology products over the next 5-10 years has the *potential to overwhelm* the U.S. regulatory system
- Regulators will face *difficult challenges* that go *beyond contained industrial uses and traditional environmental release*
- The safe use of new biotechnology products requires *rigorous, predictable, and transparent risk-analysis processes* that *mirror* the *scope, scale, complexity, and tempo* of biotechnology development
- Agencies involved in regulation of future biotechnology products would benefit from *adopting recommendations made by previous National Academies' committees*

Biotechnology Example: Biological Circuit Design

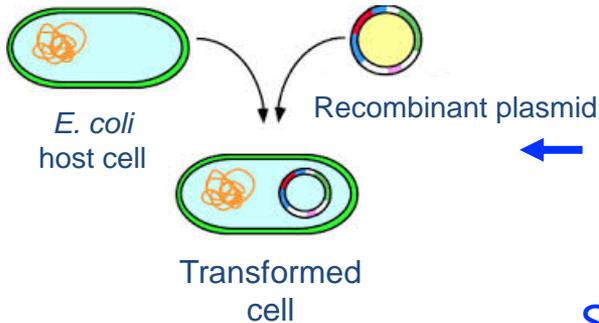


Natural organisms

Mine "parts"

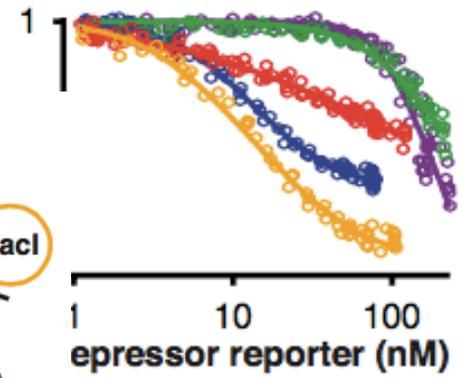
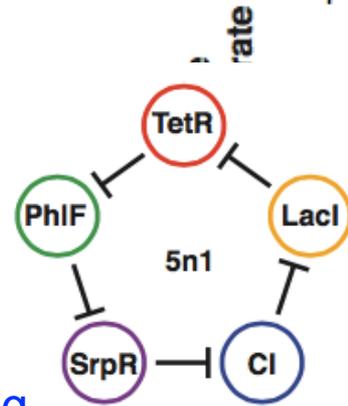
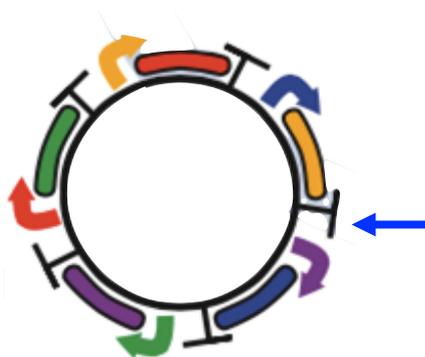


Conceive new circuits



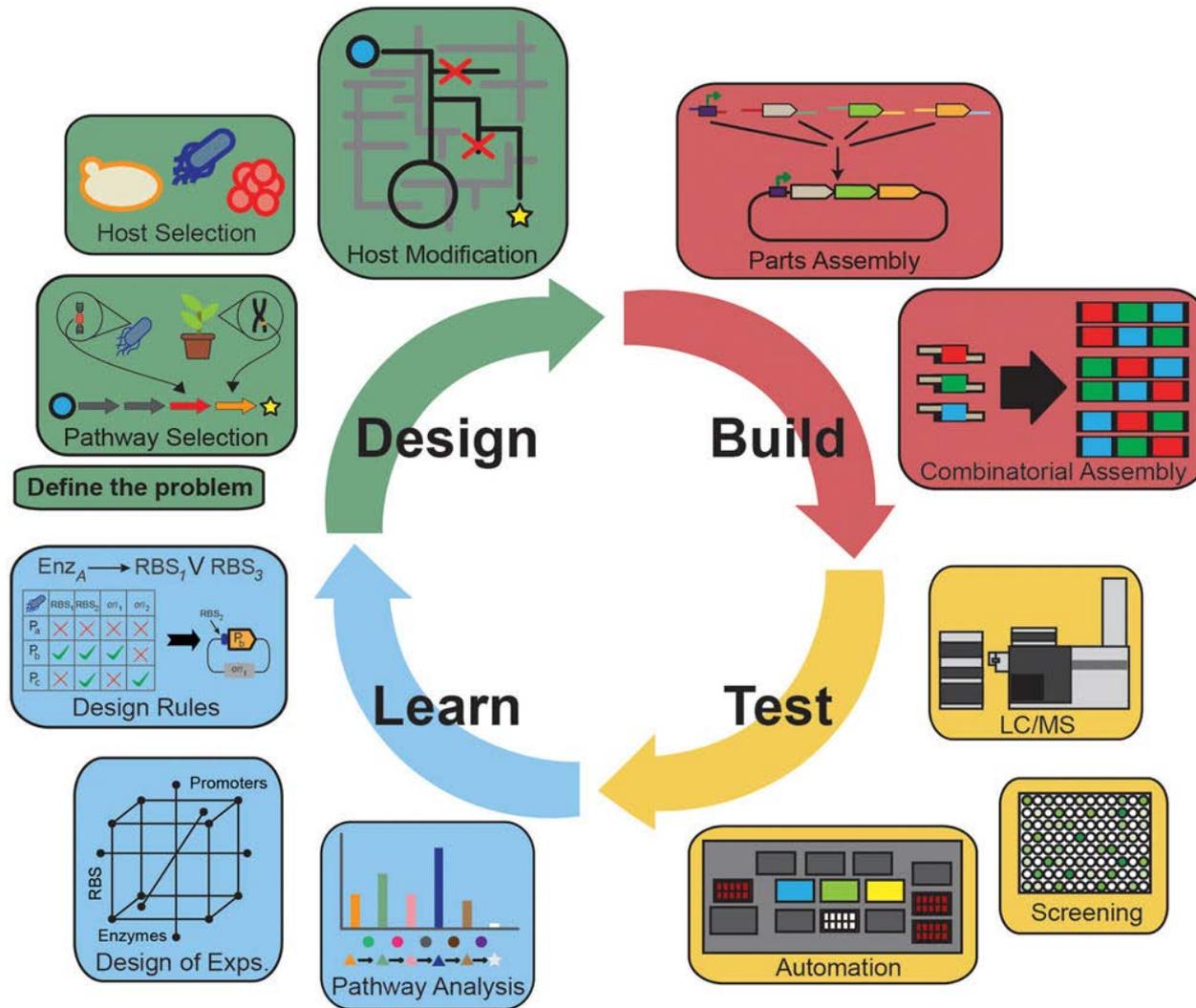
Transform circuit (plasmid) into cells

Synthesize circuit using DNA synthesis (\$0.05/bp)

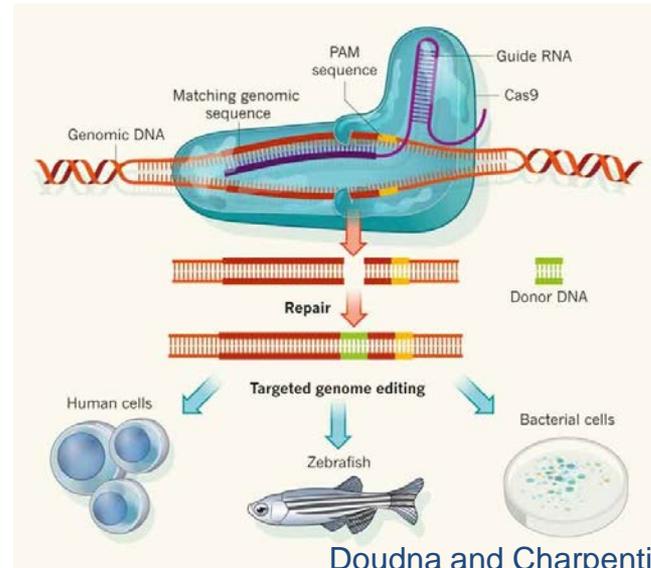
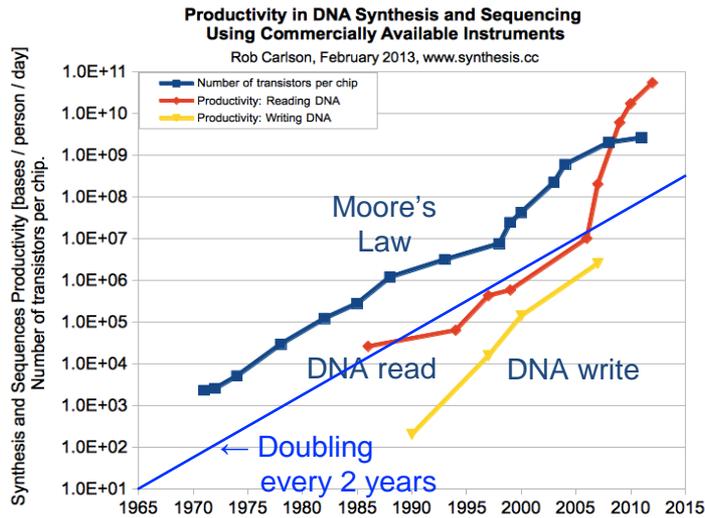


Characterize and choose specific parts to use in circuit

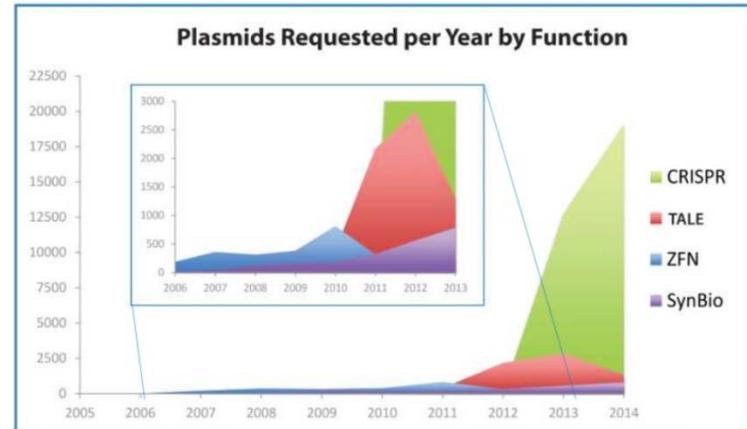
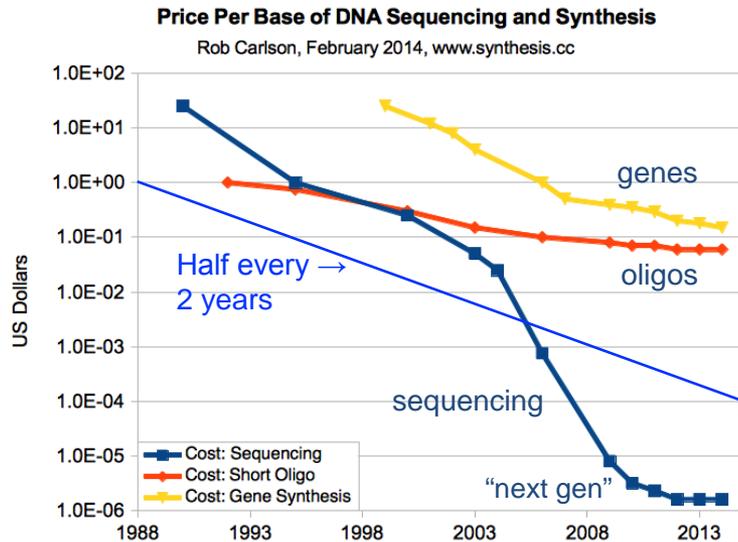
The Design-Build-Test-Learn Cycle



DNA Manipulation to Genome Editing



Doudna and Charpentier, *Nature*, 2013



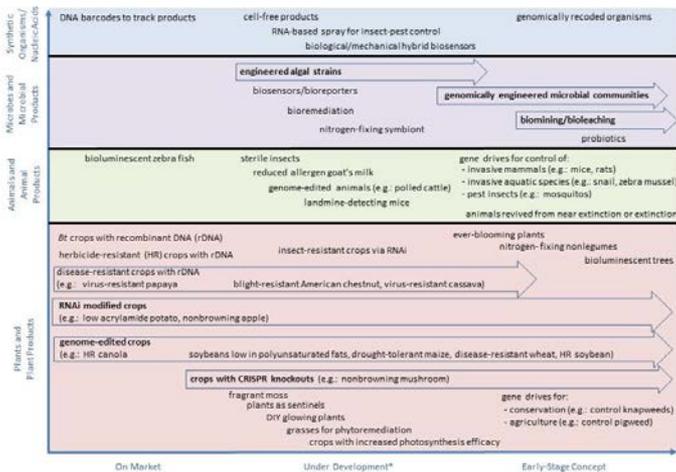
Source: Addgene, Inc.

What is a Biotechnology Product?

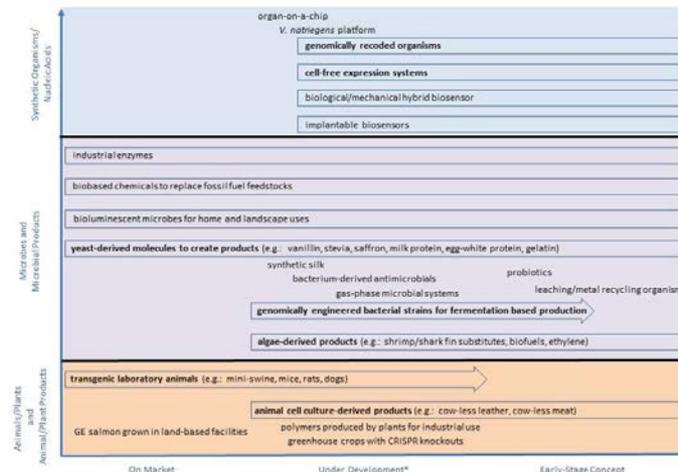
Products developed through genetic engineering or genome engineering or the targeted or *in vitro* manipulation of genetic information of organisms, including plants, animals, and microbes

- Includes products where the engineered DNA molecule is itself the “product” as in an engineered molecule used as a DNA information-storage medium
- Also covers some products produced by such plants, animals, microbes, and cell-free systems or products derived from all of the above

Open release products



Contained use products

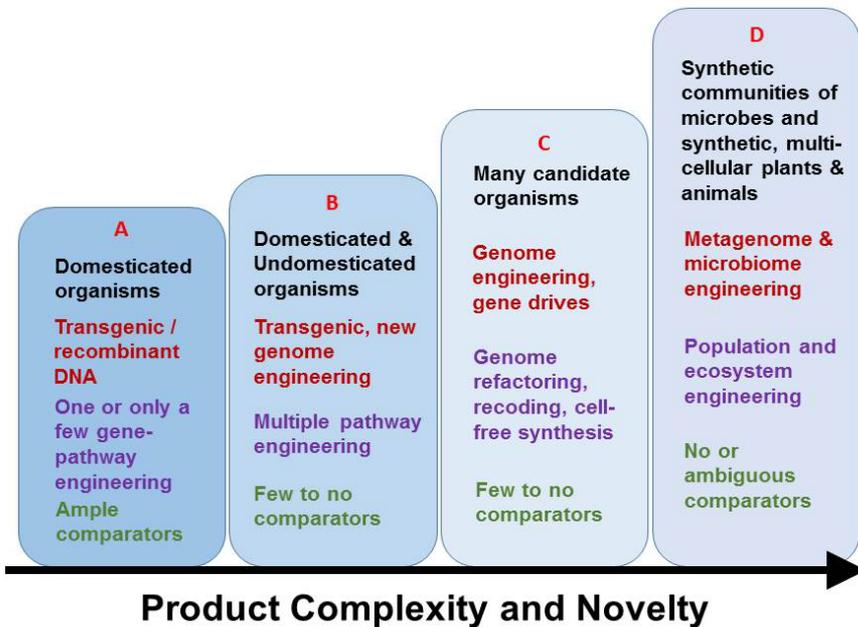


“Platforms”

(products used to make other products)

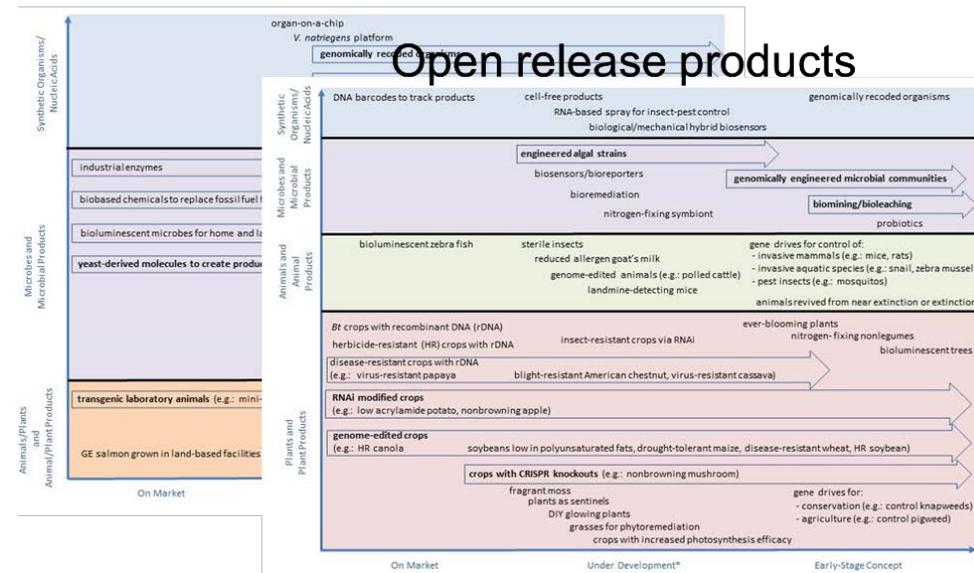
New Types of Products

The *scale, scope, complexity, and tempo* of biotechnology products are *likely to increase* in the next 5-10 years. Many products will be similar to existing biotechnology products, but they may be created through new processes, and *some products may be wholly unlike products that exist today*

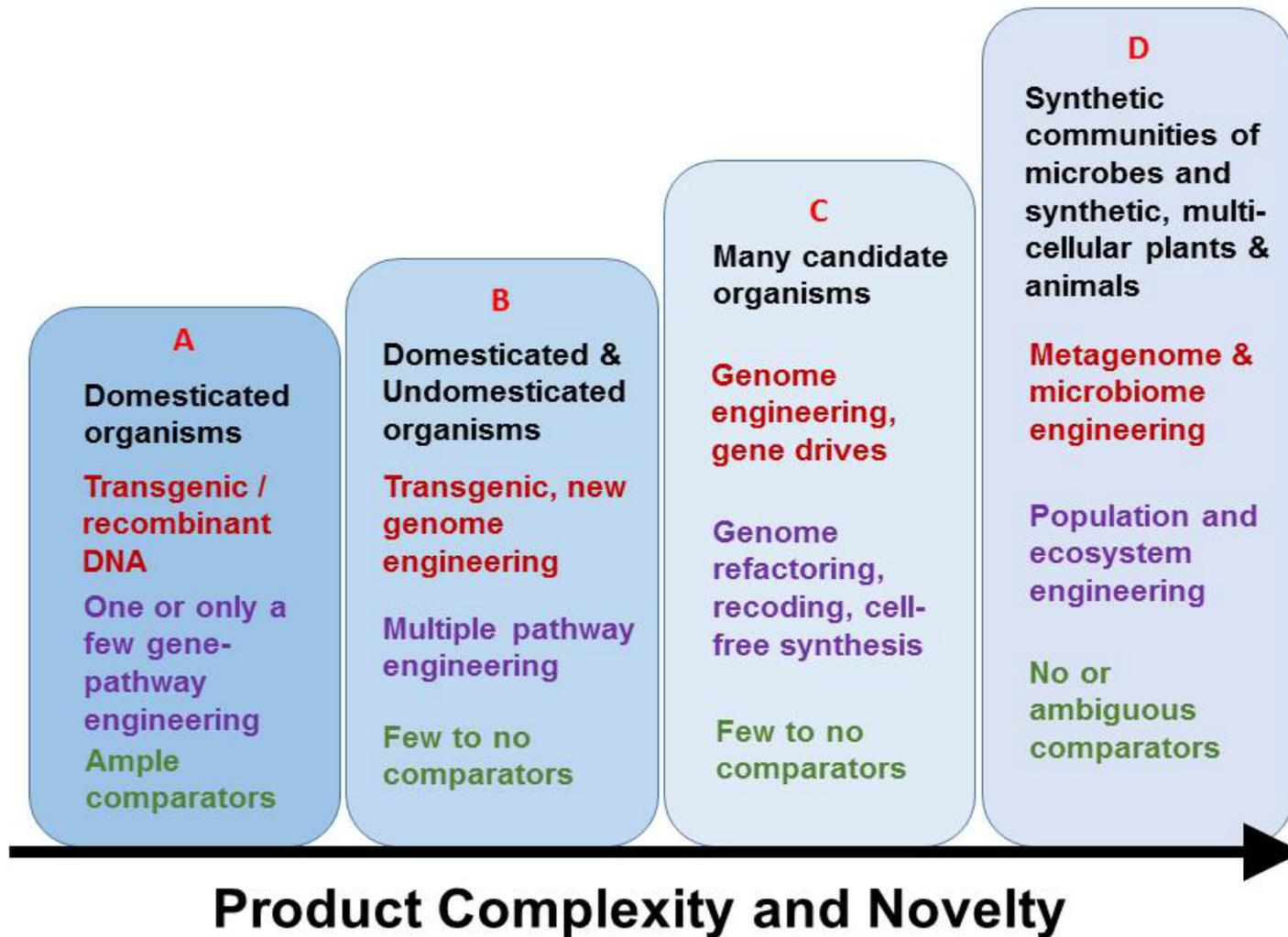


Contained use products

Open release products



New Types of Products



Open Release Products

Engineered plants, animals, microbes for deliberate release in an open environment

Open Release Products: Plants

Managed crops

- drought-tolerant corn
- virus-resistant cassava
- non-browning apple



Little/no management

- fungus-resistant American chestnut
- munitions-degrading switchgrass

Consumer appeal

- glowing plant
- fragrant moss
- ever-blooming plant

Open Release Products: Animals

Biocontrol/gene drives for:



- invasive mammals (mice, rats)
- invasive aquatic species (zebra mussel)
- pest insects (mosquitos)

Livestock with improved traits

- polled cattle
- super-muscled pigs
- allergen-free goats



De-extinction

- passenger pigeon
- woolly mammoth/cold-tolerant elephant

Open Release Products: Microbes

Biosensors

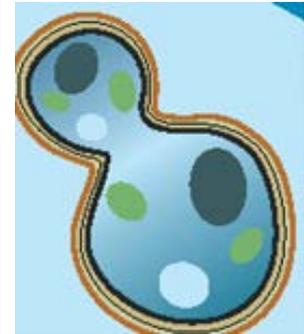
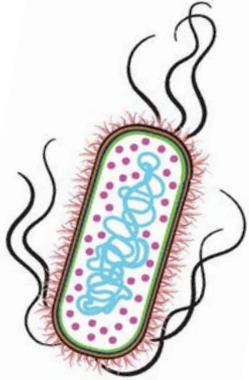
- mammalian gut tracking
- pollinator gut tracking
- arsenic detection

Microbial communities for human gut

- enriched foods
- medical purposes
- lifespan elongation

Microbial communities for crops

- nitrogen fixation
- pest management



Contained Use Products

Engineered organisms intended for use in sealed environments such as industrial fermenters, ponds, tanks, and cages

Contained Use Products

Microbially-produced

- biobased chemicals
- food additives (gelatin, egg-white, milk protein)

Algae-produced

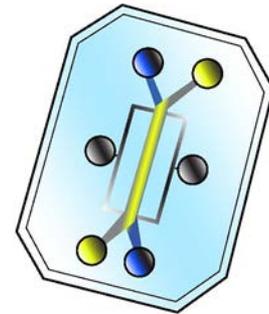
- shrimp/shark fin substitutes
- biofuels

Animals/animal-derived

- GE salmon
- cell culture-derived cowless leather & meat

Plant-derived

- polymers for industrial use (silk, collagen)



Biotechnology “Platforms”

Products intended for use in the creation of other biotechnology products, either for use in professional or “Do-It-Yourself” settings

“Wet lab”

- DNA/RNA, enzymes, cloning kits, cells

“Dry lab”

- computer-aided design software, informatics tools

Horizon Scanning

Detection of early signs of potentially important developments through a systematic examination of potential threats and opportunities, with emphasis on new technology and its potential impacts

Horizon Scanning Recommendations

- **Regulatory agencies:** develop new mechanisms for outreach to public and developer communities
- **Agencies that fund biotechnology research:** invest in regulatory science and link research and education activities to regulatory science
- **Agencies with educational missions:** invest in activities to increase awareness of the regulatory system in courses for students whose research will lead to advances in biotechnology

Horizon Scanning Progress

- USDA, EPA & FDA continue to meet regularly to coordinate activities and implement recommendations
- Following the NAS report release, USDA funded the expansion of the NAS future products database and development of an integrated horizon-scanning approach

Horizon Scanning: New Database

The screenshot shows a web browser window with the URL <https://futurebioengineeredproducts.org>. The page features the logo for Future Bioengineered Products, which includes a stylized flask with an upward-pointing arrow and the text "FUTURE BIOENGINEERED PRODUCTS" and "An open timeline of new and emerging innovations in biotechnology". A navigation bar contains "Login", "Request an account", and a search icon. The main heading is "Explore bioengineered products", followed by a paragraph explaining the database's origin and purpose. Three large colored squares (blue, green, yellow) contain icons representing different product categories: a clock for "On market", a gear for "Near commercialization", and two pills for "Early stage concept". A sidebar on the right lists "Status" and "Product Category" with corresponding icons. At the bottom, there are buttons for "APPLY FILTER" and "ADVANCED SEARCH", along with the Environmental Law Institute logo and a copyright notice for 2017.

FUTURE BIOENGINEERED PRODUCTS
An open timeline of new and emerging innovations in biotechnology

Login Request an account Search

Explore bioengineered products

This website allows you to search data originally assembled by the National Academies of Science, Engineering and Medicine for their recent report on Future Biotechnology Products. The database is being updated to support inquiries by the public, academic and industrial researchers, businesses, investors, and others interested in better understanding advances in bioengineered products.

Status

- On market
- Near commercialization
- Early stage concept

Product Category

- Food / Agriculture
- Health / Personal Care
- Industrial
- Consumer
- Other

APPLY FILTER

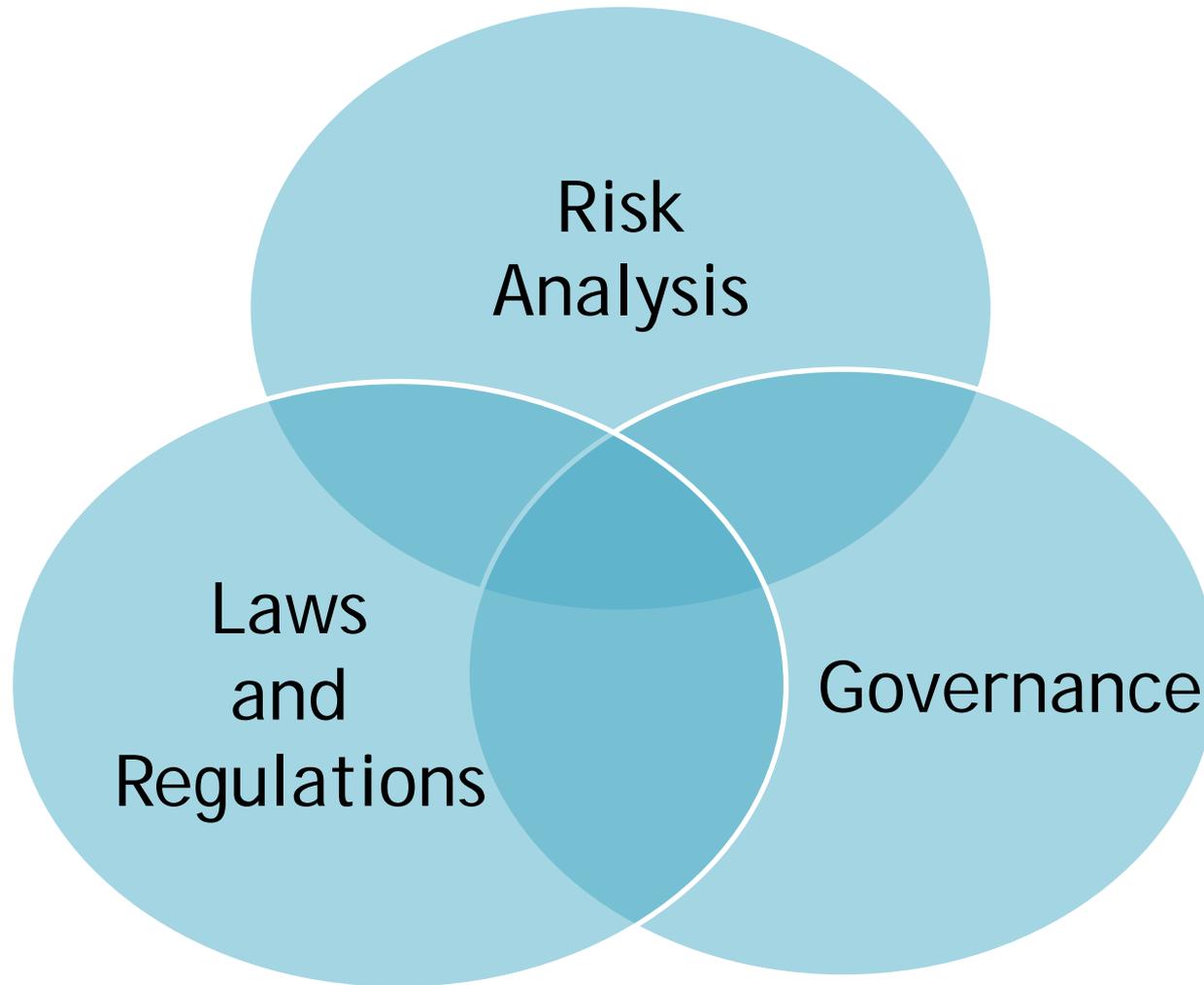
ADVANCED SEARCH

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Improve identification of novel risk pathways

Risk Analysis, Laws, and Governance



Risk Analysis

- Assessment, communication, management of human health, and environment risks
- Public, private, and non-governmental organizations and society
- Local, regional, national, or global scales.

Risk Assessment

- Probability function of exposure and effects
- Human risk assessment evaluates likelihood of adverse effects to individuals
- Ecological risk assessment “evaluates the likelihood that adverse ecological effects may occur or are occurring as a result of exposure to one or more stressors” (U.S. EPA, 1992a)
 - Effects on species, populations, communities, ecosystems

Adapted from NASEM (2017)

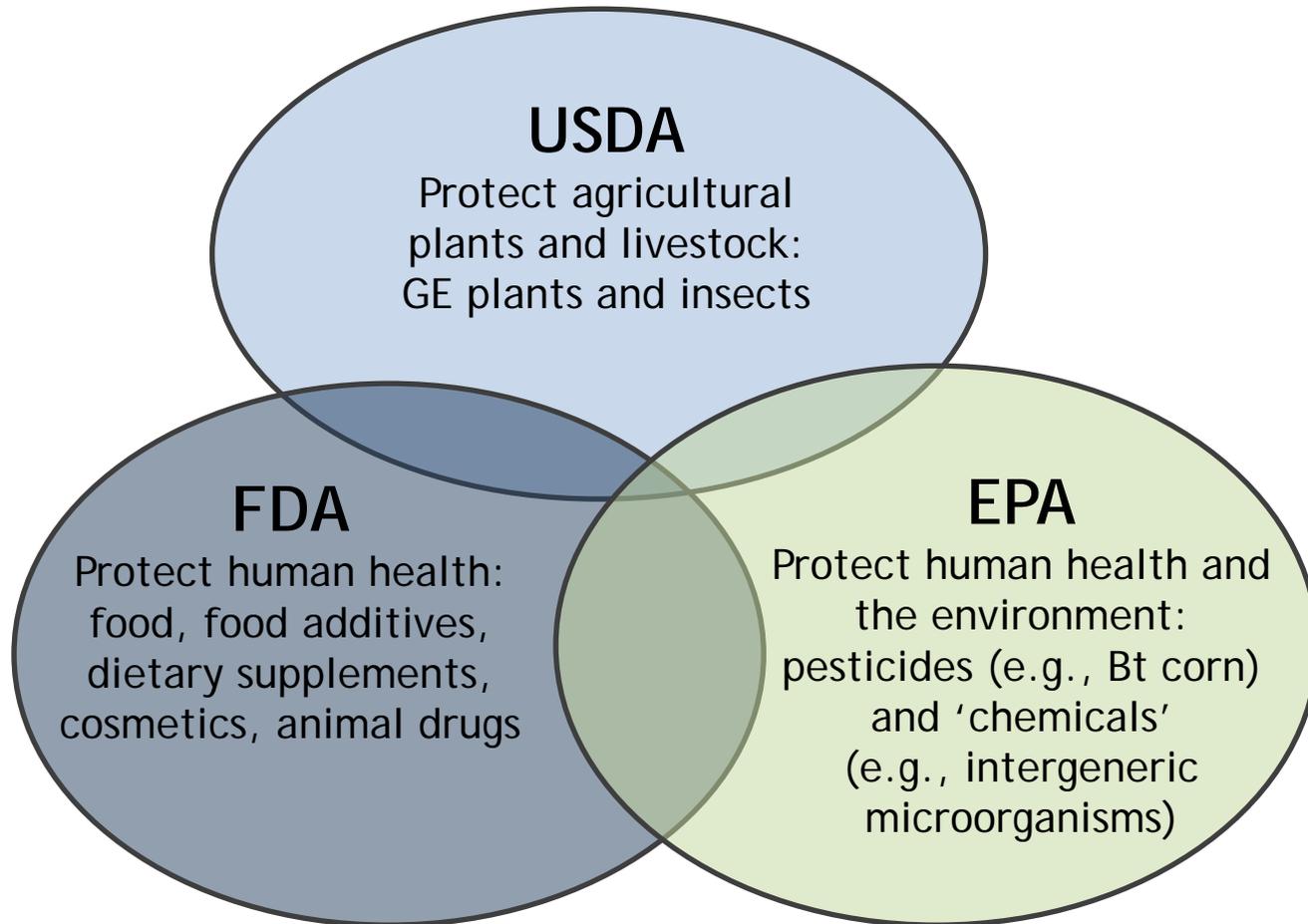
Governance

Values, norms, processes and institutions that society manages to resolve conflicts in technology development; includes public and stakeholder participation and transparent decision-making. Includes oversight (watchful and responsible care) or regulatory supervision.



Adapted from NASEM (2017)

U.S. Federal Statutes and Agencies - Coordinated Framework



Regulatory Framework

The Coordinated Framework for Regulation of Biotechnology has *considerable flexibility* to cover a wide range of biotechnology products, but in some cases the *jurisdiction of the agencies has the potential to leave gaps in regulatory oversight* for future products

The current is *complex and fragmented*, can be difficult for individuals, nontraditional organizations, and small- and medium-sized enterprises to navigate, *might cause uncertainty and a lack of predictability* for developers, and has the *potential for loss of public confidence* in regulation of future biotechnology products

Future Risk Analyses

The risk-assessment endpoints are not new, but the pathways to those endpoints have the potential to be very different in terms of complexity.

- Products used in commercial manufacturing facilities
- Products manufactured and used within the home
- Next generation plants for agriculture and ecosystem restoration
- Open release microorganisms and microbial consortia
- Open release products designed to eradicate, suppress or enhance a target species population

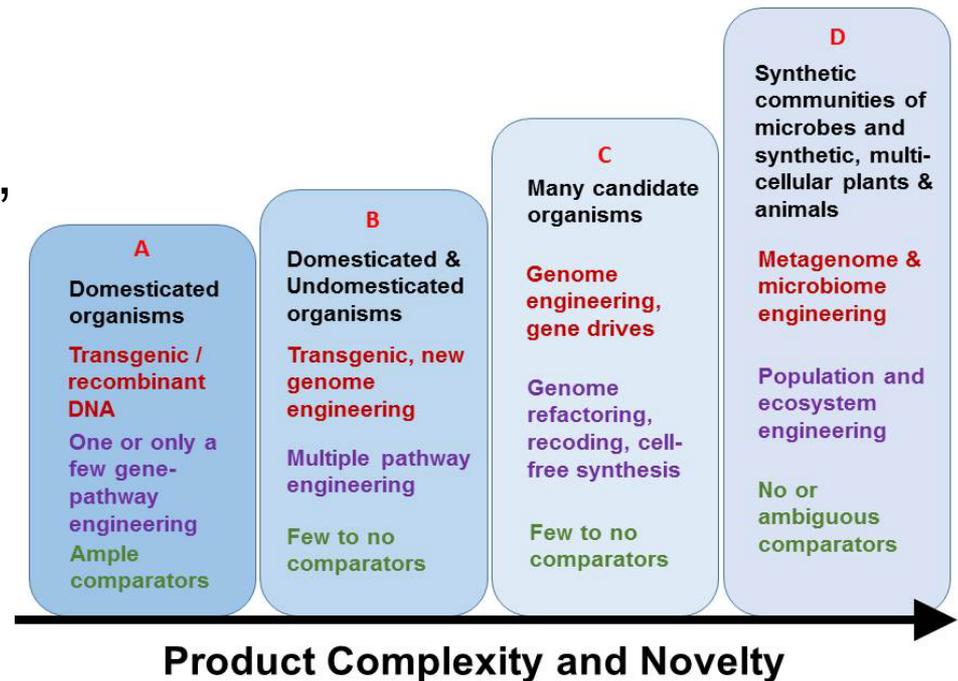
Enhancing Risk Analysis Capability

- Comparators, Off-target gene effects and Phenotypic characterization
- Gene fitness, Genetic stability, Horizontal gene transfer
- Control of organismal traits (containment and confinement)
- Physical and computational models and Life-cycle analyses
- Standardization of methods and data
- Monitoring and surveillance
- Economic and social costs and benefits

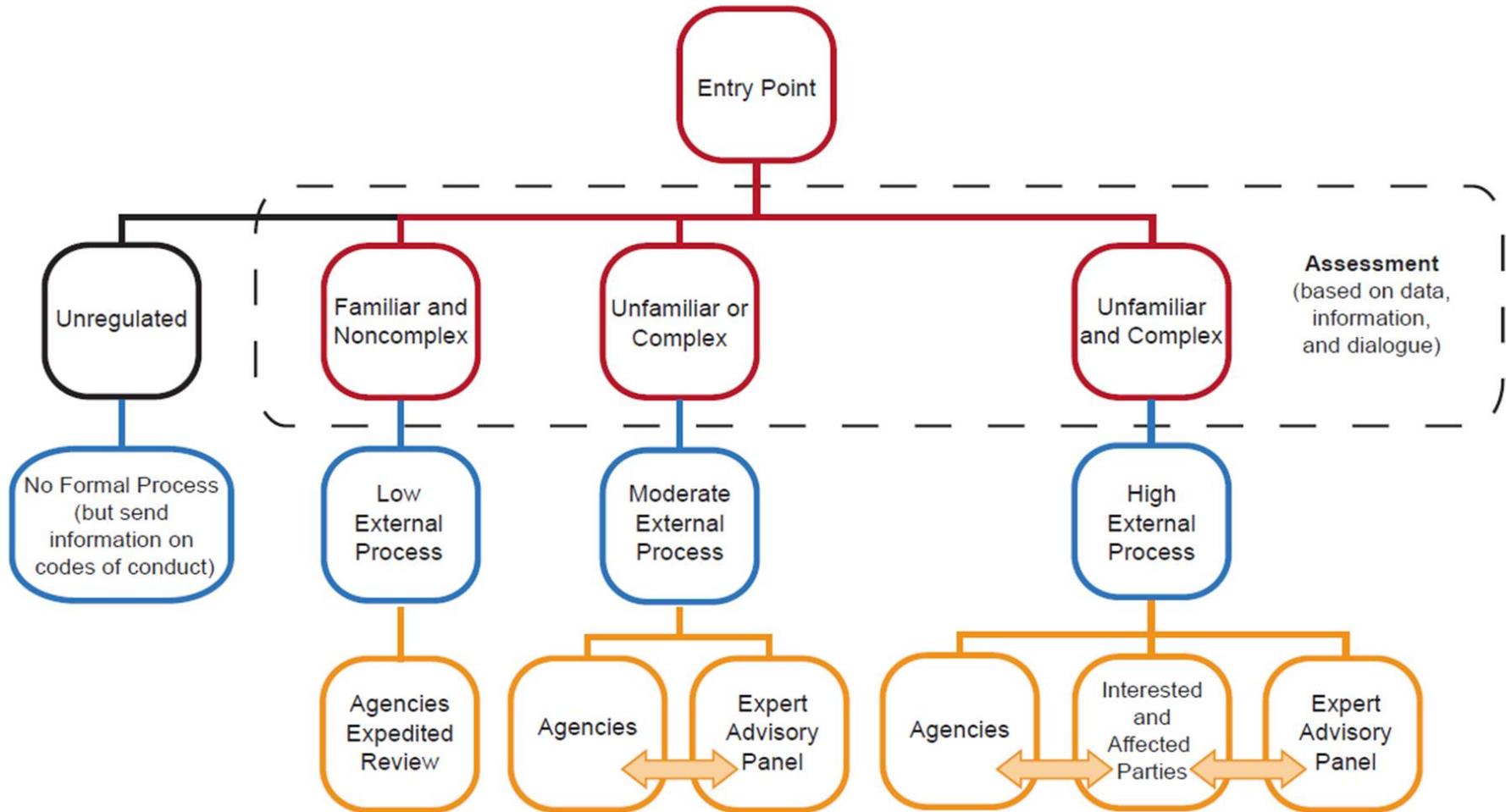
Future Regulatory Challenges

The *profusion* of future biotechnology products *will challenge* the federal agencies' ability to handle significant *increases in the rate, number, and complexity* of biotechnology products and *the diversity of actors*

To enable effective regulation, it would be beneficial to have a *single point of entry* into the regulatory system



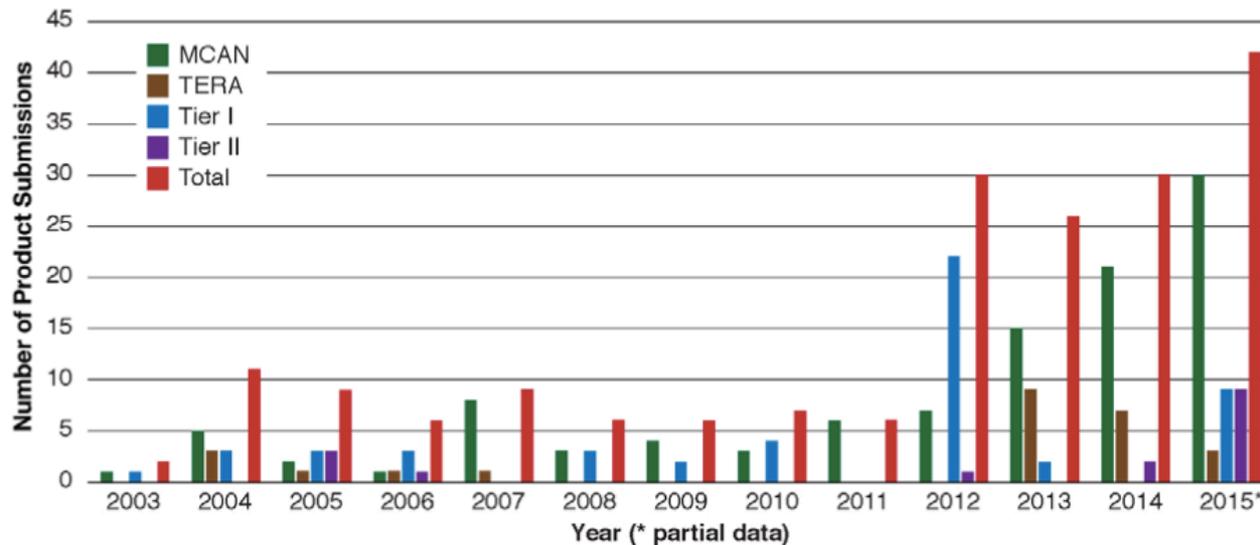
A Single Point of Entry



Example mechanism: Different ways to implement similar ideas (this is just one)

Enhancing Risk Analysis Capacity

The staffing levels, expertise, and resources available in EPA, FDA, USDA, and other agencies that have interests related to future biotechnology products *may not be sufficient to handle the expected scope and scale* of future biotechnology products.



Increase in Toxic Substances Control Act (TSCA) biotechnology product submissions to U.S. Environmental Protection Agency (EPA), 2003–15.

- MCAN = Microbial commercial activity notices;
- TERA = TSCA experimental release applications.
- Tier I exemption requires certain certifications and recordkeeping.
- Tier II exemption requires certain certifications and a notification to EPA and EPA review of specific physical containment and control technologies.

Recommendation #1

EPA, FDA, USDA and other agencies involved in regulation of future biotechnology products should *increase scientific capabilities, tools, expertise, and horizon scanning in key areas of expected growth* of biotechnology, including *natural, regulatory, and social sciences*

- Build and maintain capacity to rapidly triage products, focused on new pathways to risk-assessment endpoints
- Scan the horizon for new products that present novel risk pathways and develop new approaches to assess and address more complex risk pathways
- EPA, FDA and USDA should work together to
 - Implement mechanisms for keeping aware of the emerging technologies
 - Pilot new approaches to problem formulation, uncertainty characterization, and risk-benefit assessments
 - Pool skills and expertise across the government for first-of-a-kind cases
- Pre-competitive “data commons” to provide information to developers
- Implement a more permanent, coordinated mechanism to measure progress

Recommendation #2

EPA, FDA, and USDA should increase their use of *pilot projects* to *advance understanding and use of ecological risk assessments and benefit analyses* for future biotechnology products that are unfamiliar and complex and to *prototype new approaches for iterative risk analyses that incorporate external peer review and public participation*

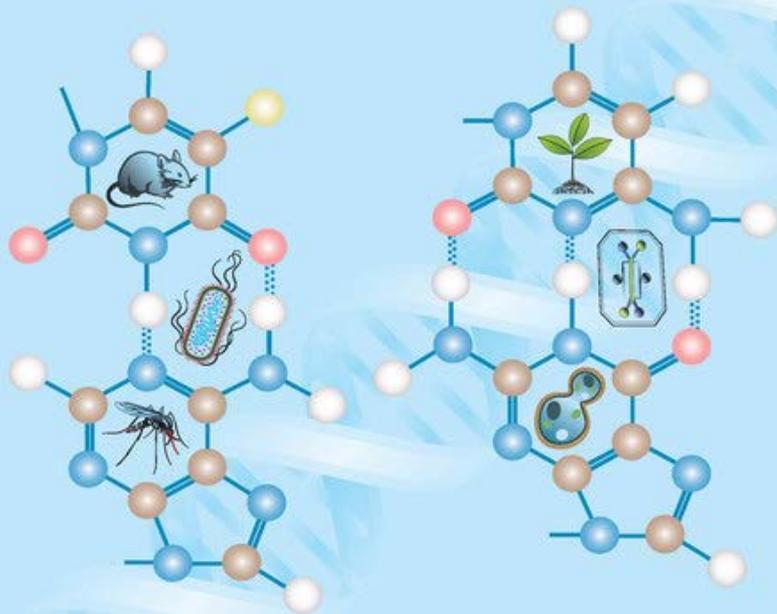
- More iterative processes for risk assessments that span development cycles
- Advances in ecological risk assessments/benefit analyses for open-release products
- Probabilistic estimates of risk to assess likelihood of adverse effects of future biotechnology products compared to existing alternatives
- New methods of outreach to the public and developer community (horizon scanning, capability growth, improving understanding)
- Engage with federal and state consumer and occupational safety regulators

Recommendation #3

The National Science Foundation, the Department of Defense, the Department of Energy, the National Institute of Standards and Technology, and other agencies that fund biotechnology research with the potential to lead to new biotechnology products should *increase their investments in regulatory science and link research and education activities to regulatory-science activities*

- Develop long-term strategy for risk analysis of future biotechnology products
- Establish appropriate federal funding levels for sustained, multi-year research to develop the necessary advances in regulatory science
- Provide linkages to market-path requirements for regulatory success
- Invest in new methods of understanding ethical, legal, and social implications associated with future biotechnology products
- Increase graduate and post-graduate knowledge of the regulatory system

Preparing for Future Products of Biotechnology



Thank you!

This study was sponsored by the U.S. Environmental Protection Agency, the U.S. Food and Drug Administration, and the U.S. Department of Agriculture.

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Questions?

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