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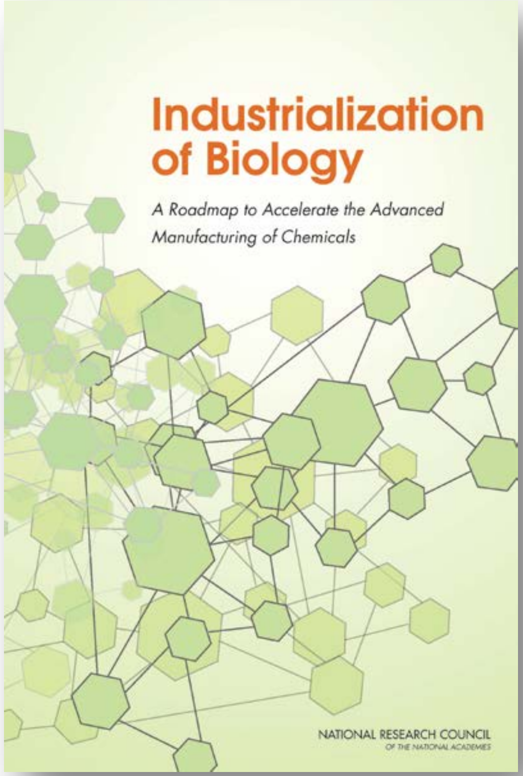
Industrialization of Biology:

A Roadmap to Accelerate the Advanced Manufacturing of Chemicals



Douglas Friedman

Board on Chemical Sciences and Technology
Board on Life Sciences

DOE Biological & Environmental Research
Advisory Committee Meeting

October 29, 2015

Statement of Task

In order to realize the full benefit of research investments intended to enable the advanced manufacturing of chemicals using biological systems, an ad hoc committee will develop a roadmap of necessary advances in basic science and engineering capabilities, including knowledge, tools, and skills. Working at the interface of synthetic chemistry, metabolic engineering, molecular biology, and synthetic biology, the committee will

Essential elements of the roadmap that the committee will consider in the study and in its report, include the following:

- identification of the core scientific and technical challenges that must be overcome;
- identification of and timeline for tools, measurement techniques, databases, and computational techniques needed to serve as the building blocks for research and applications;
- how to develop, share, and diffuse common interoperable standards, languages, and measurements; and
- when and how to integrate nontechnological insights and societal concerns into the pursuit of the technical challenges.

challenges, knowledge, tools, and systems needed to advance the science and engineering required for advanced manufacturing of chemicals using biological systems and to develop the workforce required to realize these advances. The report will not include recommendations related to funding, government organization, or policy issues.

Study Committee & Staff

Committee

Thomas M. Connelly (*Chair*), E.I. du Pont de Nemours & Company (Ret.)

Michelle C. Chang, University of California, Berkeley

Lionel Clarke, UK Synthetic Biology Leadership Council

Andrew D. Ellington, University of Texas at Austin

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Stephen S. Laderman, Agilent Technologies, Inc.

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Kathie L. Olsen, ScienceWorks, LLC
Markus Pompejus, BASF Corporation

The review of this report was overseen by **Klavs F. Jensen**, NAE, Massachusetts Institute of Technology, and **Michael R. Ladisch**, NAE, Purdue University.

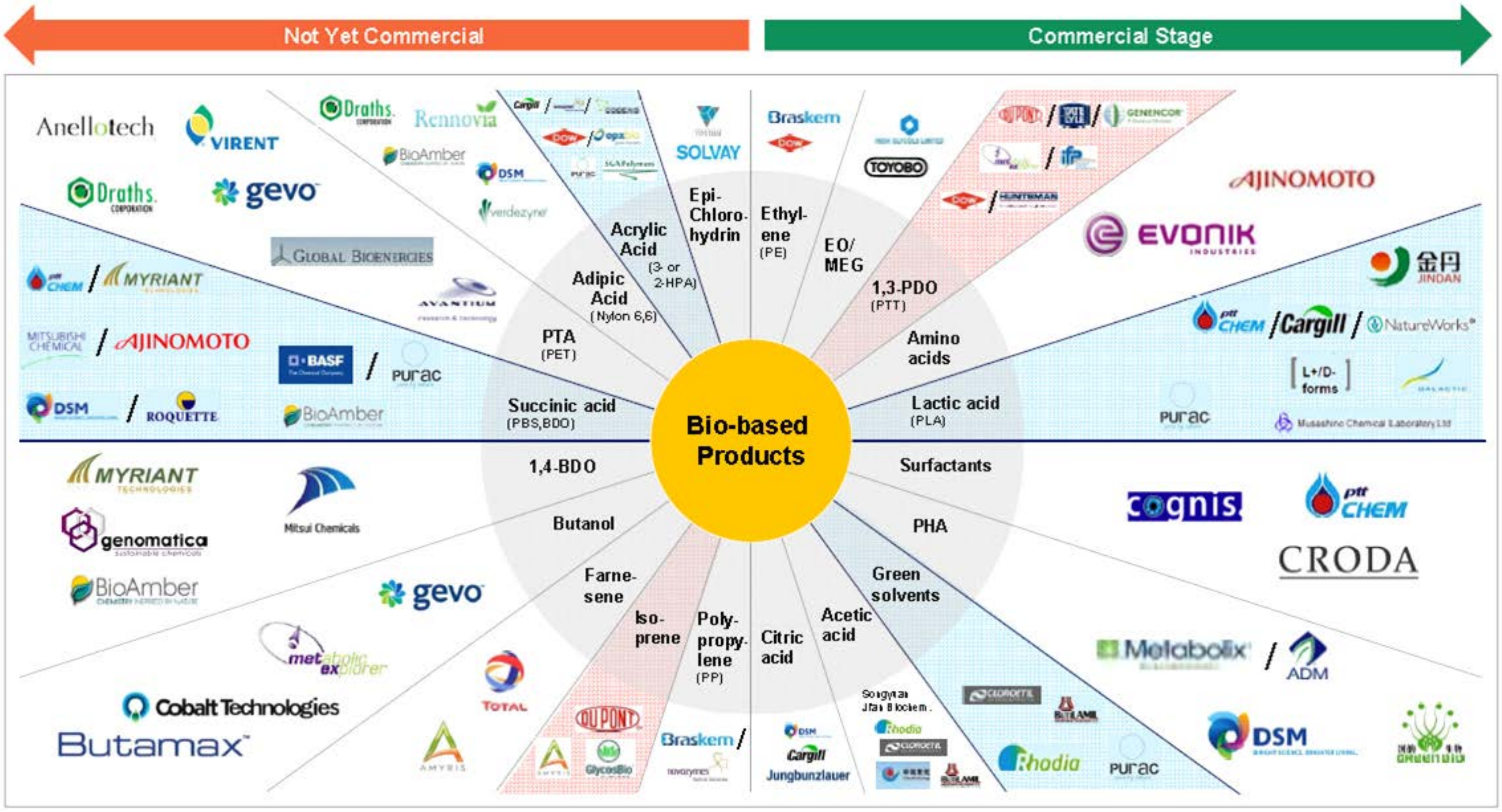
Data-Gathering Overview

- **Committee Knowledge & Experience**
  - A group of experts with broad and varied experience, representing industrial, academic, and legal experience.
- **Data-gathering conducted at 2 committee meetings plus:**
- **Information Gathering Workshop**
  - May 28-29, 2014 at the National Academies; approximately 50 participants representing a broad range of stakeholders.
  - During open sessions committee heard from a wide range of stakeholders
- **Peer-reviewed research literature**
- **Community input through study website**

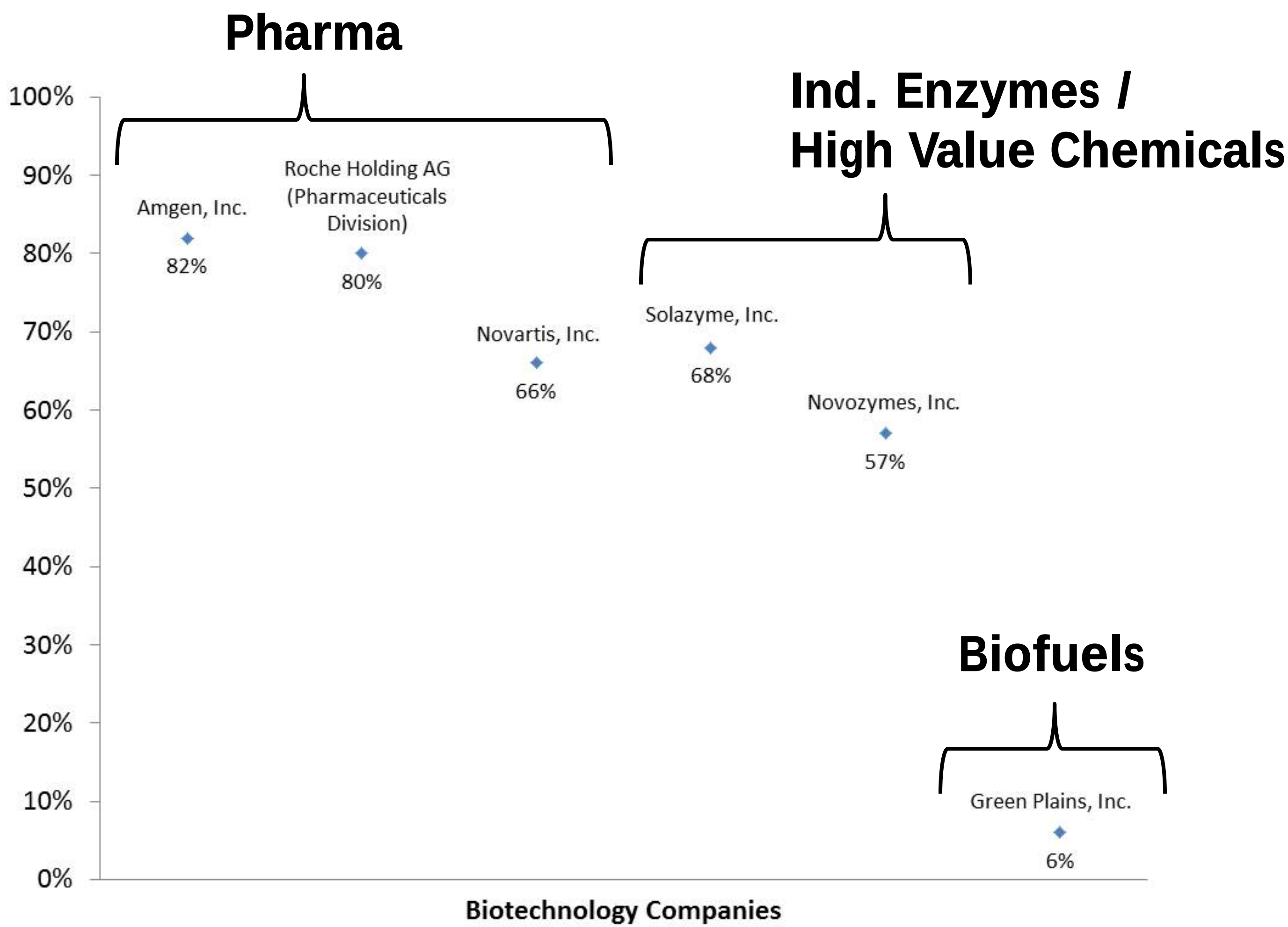
Why Now?

- Bio-based product markets are already significant in the United States, representing more than **2.2 percent of gross domestic product in 2012**.
- Current global bio-based chemical and polymer production is estimated to be **about 50 million tons each year**.
- The manufacturing of chemicals using biological synthesis and engineering **could expand even faster**: the addition of new bio-based routes to chemicals could open the door to making and marketing chemicals that cannot presently be made at scale or may allow the use of new classes of feedstocks.

Biomaterials Competitive Landscape



Gross Margin of Representative Companies



Considerations for Specialty vs Large-Volume

SPECIALTY CHEMICALS
-Examples
-Industrial Enzymes
-Pharma Intermediaries
-Small volume
-Small assets
-Aerobic fermentation
-High value add
-High purity, high separations cost

LARGE-VOLUME CHEMICALS
-Examples
-Biofuels
-Polymer intermediates
-Moderate to large volume
-Asset intensive
-Anaerobic and aerobic fermentation
-Feedstock costs important
-Large fermentation scale
-Large volumes of water and cell-mass co-product

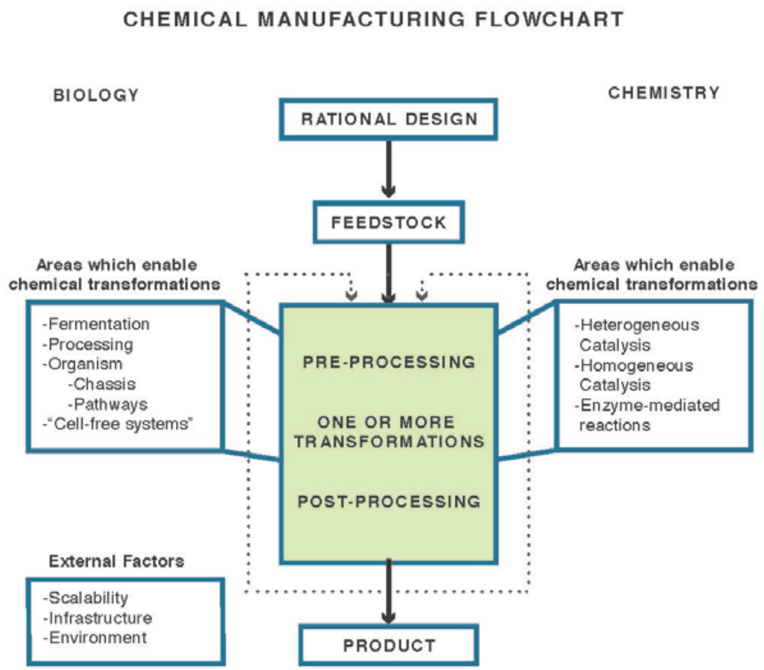
SHARED ENABLING SCIENCE AND ENGINEERING

Why Now?

- **Science is Advancing**: The past decade has seen an explosion in the technologies to compose, read, write, and debug DNA. This has rapidly **increased the scale and sophistication of genetic engineering projects**, and in the near term this will lead to more complex chemical structures and composite nanomaterials, which require precise control over dozens of genes.
- **Industry is Ready**: **Increasing use of biology** to produce high-valued chemical products that cannot be produced at high purity and high yield through traditional chemical synthesis, as well as increased production of high-volume chemicals in cases where biology represents a **better synthetic pathway** (cheaper and greener) than the conventional chemical synthesis.

A Vision of the Future

- **Chemical Manufacturing**: The visions is one where biological synthesis and engineering and chemical synthesis and engineering are *on par with one another* for chemical manufacturing.



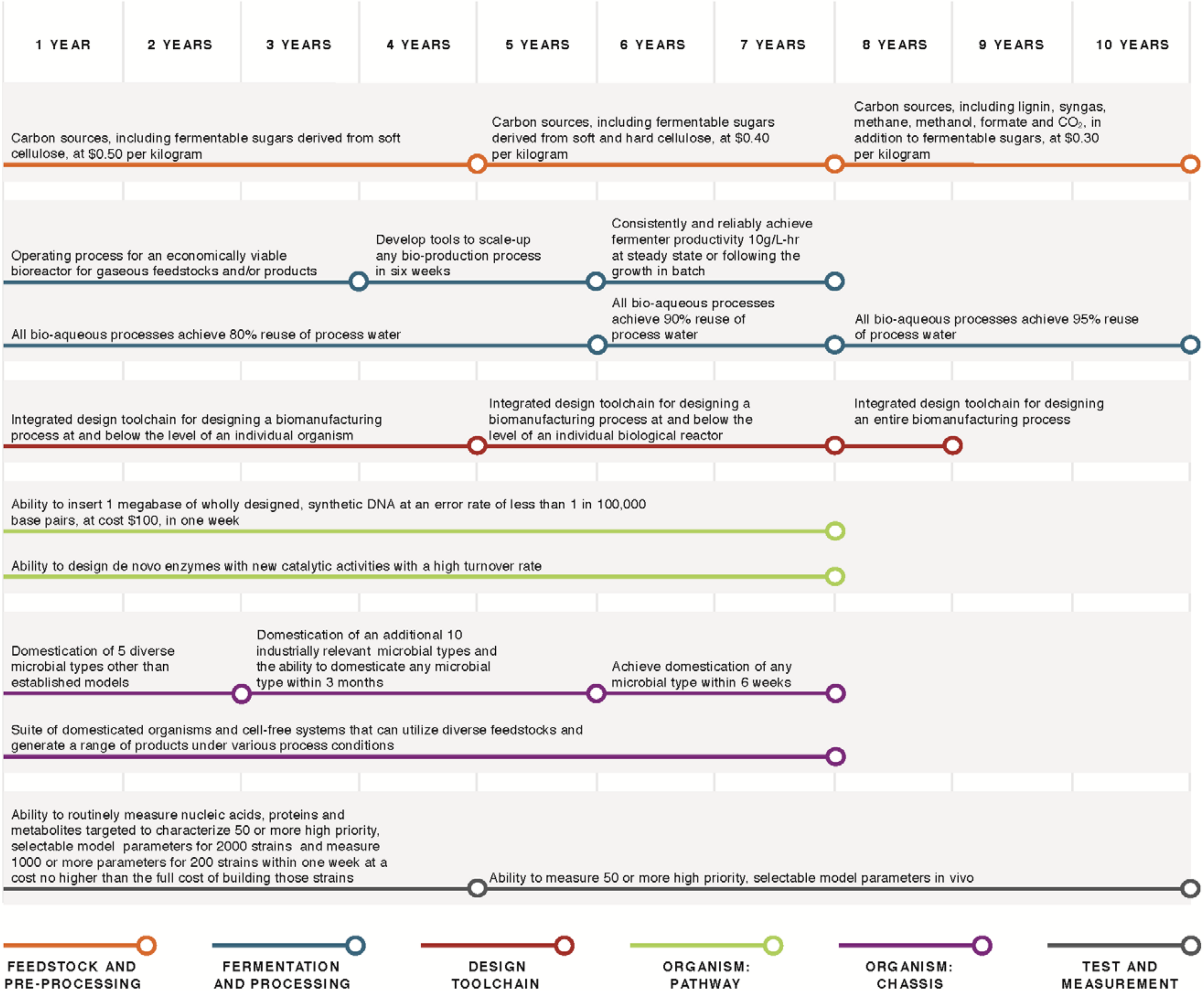
A Vision of the Future

- **Energy**: Advanced chemical manufacturing based on biological sources such as plants, algae, bacteria, yeast, filamentous fungi, and other organisms can replace many chemicals now derived from petroleum or other fossil fuels. If properly designed, bio-based production processes, including new bio-based inputs, **can improve energy efficiency and, in some cases, reduce energy costs**.
- **Environment**: Bio-based production, properly designed and managed, has the potential for **generating fewer toxic by-products and less waste** than traditional chemical manufacturing.
- **Agriculture**: The increased use of biomass as a feedstock for the production both of high-value, low-volume bio-based chemicals and bioplastics and of low-value, high-volume bulk biofuels and commodity chemicals provides **new opportunities for innovation in sustainable agriculture**. Integrated production facilities that offer the ability to produce not only biofuels but **also bio-based chemicals and bioplastics** are becoming increasingly feasible technologically and economically viable.

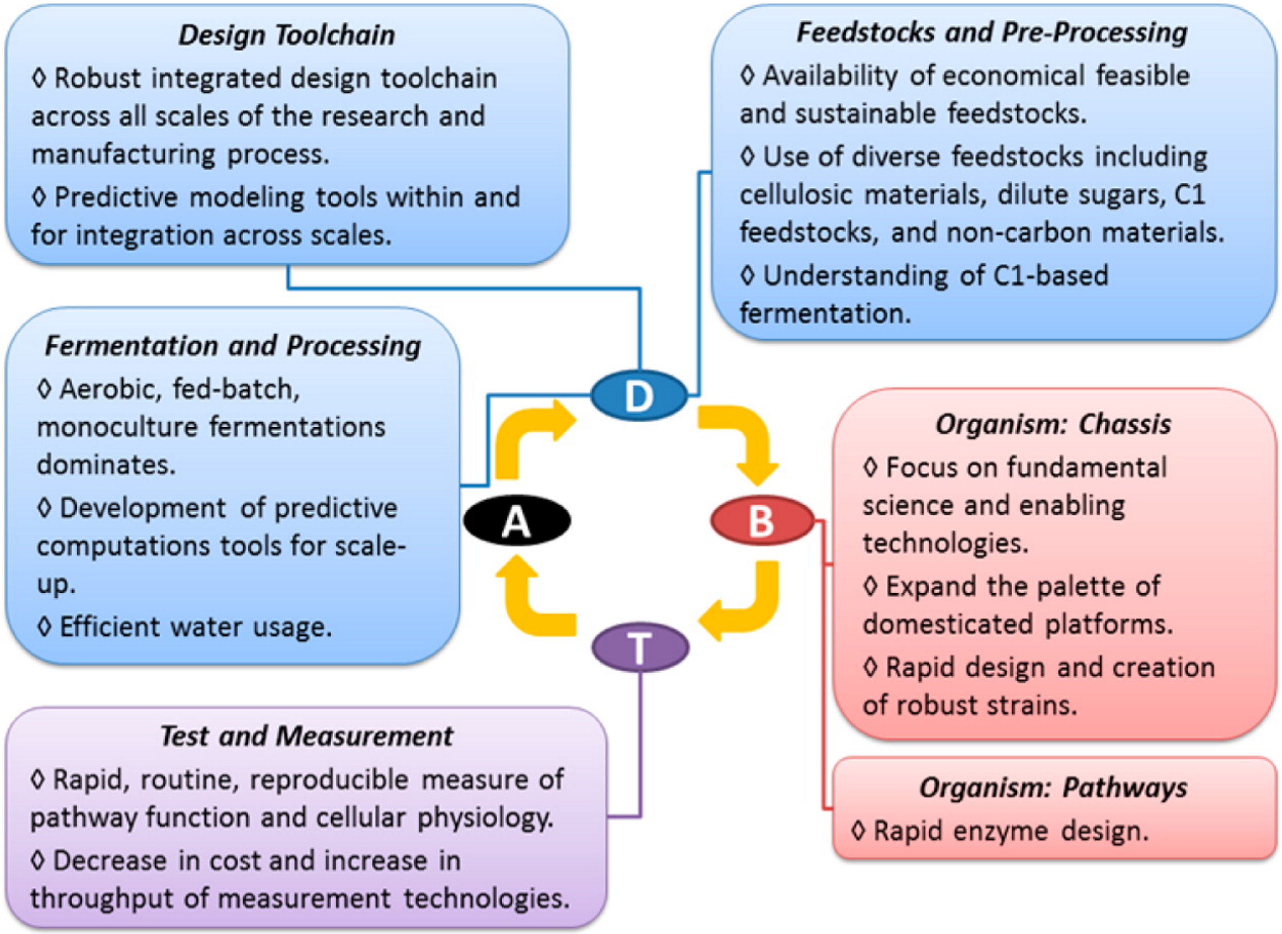
Core Technical Conclusion

Biomanufacturing of chemicals is already a **significant element of the national economy** and is poised for rapid growth during the next decade. Both the scale and scope of biomanufacturing of chemicals will expand and will involve **both high-value and high-volume chemicals**. Progress in the areas identified in the report will play a major role in achieving the challenge of increasing the contribution of biotechnology to the national economy.

*While the roadmap is clearly designed to push forward industrial biotechnology, there are many aspects of **fundamental research** that are needed, and described in this report, that can be applied broadly to other fields, such as health, energy, and agriculture.*


1 YEAR
2 YEARS
3 YEARS
4 YEARS
5 YEARS
6 YEARS
7 YEARS
8 YEARS
9 YEARS
10 YEARS
Carbon sources, including fermentable sugars derived from soft cellulose, at $0.50 per kilogram
Carbon sources, including fermentable sugars derived from soft and hard cellulose, at $0.40 per kilogram
Carbon sources, including lignin, syngas, methane, methanol, formate and CO_2, in addition to fermentable sugars, at $0.30 per kilogram
Operating process for an economically viable bioreactor for gaseous feedstocks and/or products
Develop tools to scale-up any bio-production process in six weeks
Consistently and reliably achieve fermenter productivity 10g/L-hr at steady state or following the growth in batch
All bio-aqueous processes achieve 80% reuse of process water
All bio-aqueous processes achieve 90% reuse of process water
All bio-aqueous processes achieve 95% reuse of process water
Integrated design toolchain for designing a biomanufacturing process at and below the level of an individual organism
Integrated design toolchain for designing a biomanufacturing process at and below the level of an individual biological reactor
Integrated design toolchain for designing an entire biomanufacturing process
Ability to insert 1 megabase of wholly designed, synthetic DNA at an error rate of less than 1 in 100,000 base pairs, at cost $100, in one week
Ability to design de novo enzymes with new catalytic activities with a high turnover rate
Domestication of 5 diverse microbial types other than established models
Domestication of an additional 10 industrially relevant microbial types and the ability to domesticate any microbial type within 3 months
Achieve domestication of any microbial type within 6 weeks
Suite of domesticated organisms and cell-free systems that can utilize diverse feedstocks and generate a range of products under various process conditions
Ability to routinely measure nucleic acids, proteins and metabolites targeted to characterize 50 or more high priority, selectable model parameters for 2000 strains and measure 1000 or more parameters for 200 strains within one week at a cost no higher than the full cost of building those strains
Ability to measure 50 or more high priority, selectable model parameters in vivo
FEEDSTOCK AND PRE-PROCESSING
FERMENTATION AND PROCESSING
DESIGN TOOLCHAIN
ORGANISM: PATHWAY
ORGANISM: CHASSIS
TEST AND MEASUREMENT

Key Elements Mapped to DBTA



Douglas C. Friedman; Andrew D. Ellington; *ACS Synth. Biol.* **2015,** 4, 1053-1055.

Technical Roadmap
Recommendations

- In order to transform the pace of industrial biotechnology by enabling commercial entities to develop new biomanufacturing processes, the National Science Foundation (NSF), Department of Energy, National Institutes of Health, National Institute of Standards and Technology, Department of Defense, and other relevant agencies **should support the scientific research and foundational technologies required** to advance and to integrate the areas of feedstocks, organismal chassis and pathway development, fermentation, and processing.

- The Committee recommends that the relevant government agencies consider establishment of an **on-going road-mapping mechanism** to provide direction to technology development, translation and commercialization at scale.

Economic, Education and Workshop Recommendations

- The US Government should perform a **regular quantitative measure** of the contribution of bio-based production processes to the U.S. economy to develop a capacity for forecasting and assessing economic impact.

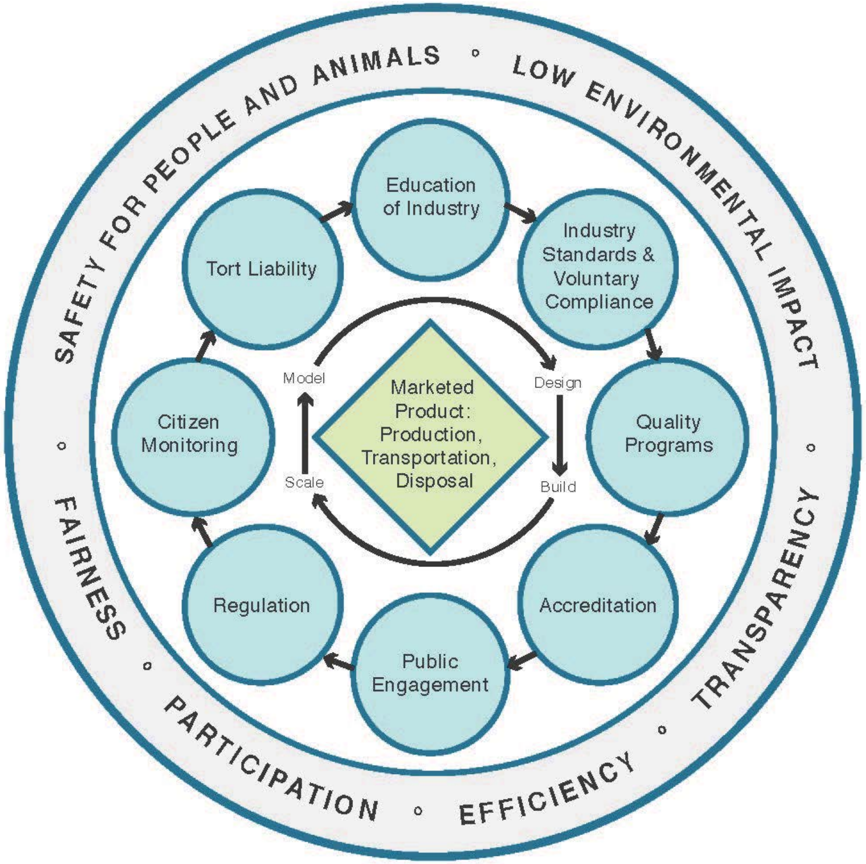
- **Industrial biotechnology** firms individually, and especially through industry groups, should **strengthen their partnerships** with all levels of academia, from community colleges, undergraduate, and graduate institutions, to communicate changing needs and practices in industry in order to inform academic instruction.

- Federal agencies, academia, and industry should devise and support innovative approaches toward expanding the exposure of student trainees to design-build-test-learn paradigms in a high-throughput fashion and **at industrial scale**.

Governance Recommendations

- The administration should ensure that the Environmental Protection Agency (EPA), U.S. Department of Commerce, USDA, Food and Drug Administration (FDA), Occupational Safety and Health Administration (OSHA), National Institute of Standards and Technology (NIST) and other relevant agencies work together to **broadly assess, and regularly reassess, the adequacy of existing governance**, including but not limited to regulation, and to identify places where industry, academia, and the public can contribute to or participate in governance.

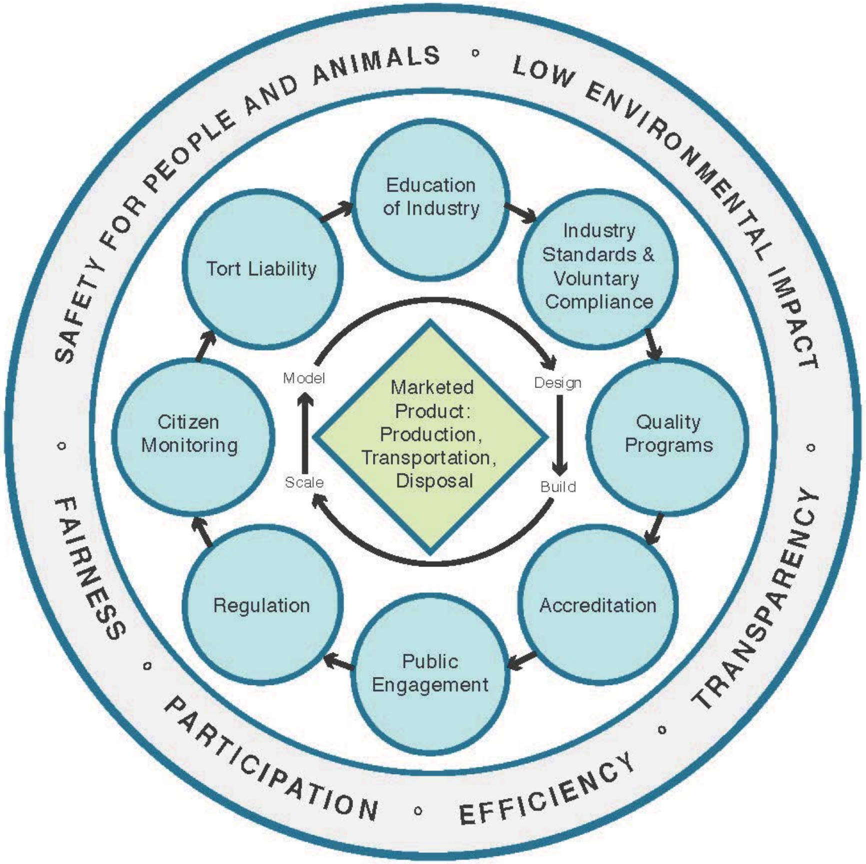
- Science funding agencies and science policy offices should **ensure outreach efforts that facilitate responsible innovation** by enabling the extension of existing relevant regulatory practices, concordance across countries, and increased public engagement.



Governance

Recommendations

- Government agencies, including EPA, USDA, FDA, and the National Institute of Standards and Technology should establish **programs for both the development of fact-based standards and metrology for risk assessment** in industrial biotechnology, and programs for the use of these fact-based assessments in evaluating and updating the governance regime.



Acknowledgments

The committee thanks all of the individuals who shared information with it during the study process, as well as those who reviewed the draft report.

The committee particularly thanks the National Science Foundation and the U.S. Department of Energy for sponsoring this study.

Download the report at http://www.nap.edu/IndBio

NSF

U.S. DEPARTMENT OF ENERGY

Office of Science