Woodrow Wilson International Center for Scholars

NEW LIFE, OLD BOTTLES

REGULATING FIRST-GENERATION PRODUCTS OF SYNTHETIC BIOLOGY

SYNBIO 2 / MARCH 2009

Synthetic BIOLOGY PROJECT

Acronyms

Present in: New Life/Old Bottles

APHIS . . . . .Animal and Plant Health Inspection Service

DNA . . . . . .Deoxyribonucleic acid

EPA . . . . . .Environmental Protection Agency

EU . . . . . .European Union

FDA . . . . . .Food and Drug Administration

FDCA . . . . .Federal Food, Drug, and Cosmetic Act

FIFRA . . . . .Federal Insecticide, Fungicide and Rodenticide Act

IBC. . . . . .Institutional Biosafety Committee

MCAN . . . . .Microbial Commercial Activity Notice

MIT . . . . . .Massachusetts Institute of Technology

NEPA . . . . .National Environmental Policy Act

NIH . . . . . .National Institutes of Health

OSTP . . . . .White House Office of Science and Technology Policy

RAC . . . . . .Recombinant DNA Advisory Committee

RDNA . . . . .Recombinant DNA

RGs . . . . . .Risk Groups

TERA . . . . .TSCA Experimental Release Application

TSCA . . . . .Toxic Substances Control Act

USDA . . . . .US Department of Agriculture

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Michael Rodemeyer

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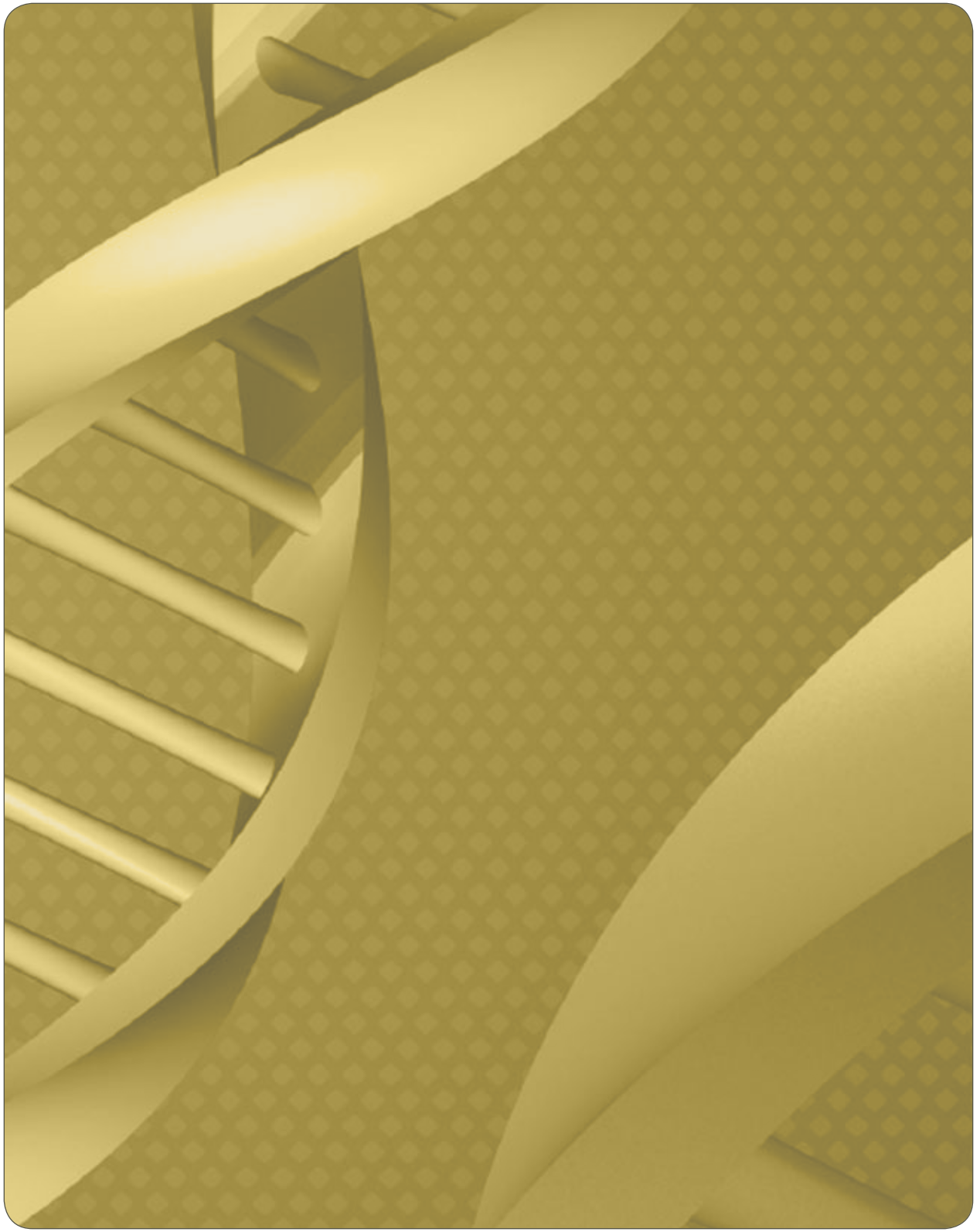


About the Author

From 2000 until 2005, Mr. Rodemeyer was the Executive Director of the Pew Initiative on Food and Biotechnology, a nonprofit research and education project on genetically modified foods funded by a grant from The Pew Charitable Trusts. Before that, Mr. Rodemeyer held a variety of posts in the federal government, including Assistant Director for Environment in the Office of Science and Technology Policy in the Clinton administration and Chief Democratic Counsel for the U.S. Congress House Committee on Science and Technology. From 1976 through 1984, Mr. Rodemeyer was an attorney with the Federal Trade Commission, working on consumer protection and antitrust issues.

Currently, Mr. Rodemeyer is an independent consultant and writer on science, technology and environmental policy. He is also an adjunct instructor in the Science, Technology and Society Department in the School of Engineering and Applied Sciences at the University of Virginia and has previously taught congressional and environmental policymaking at the Johns Hopkins University's Zanvyl Krieger School of Arts and Sciences. He has lectured widely on technology and environmental policy issues.

Mr. Rodemeyer graduated with honors from Harvard Law School in 1975 and received his undergraduate degree from Princeton University in 1972. He lives in Charlottesville, Virginia.

Foreword

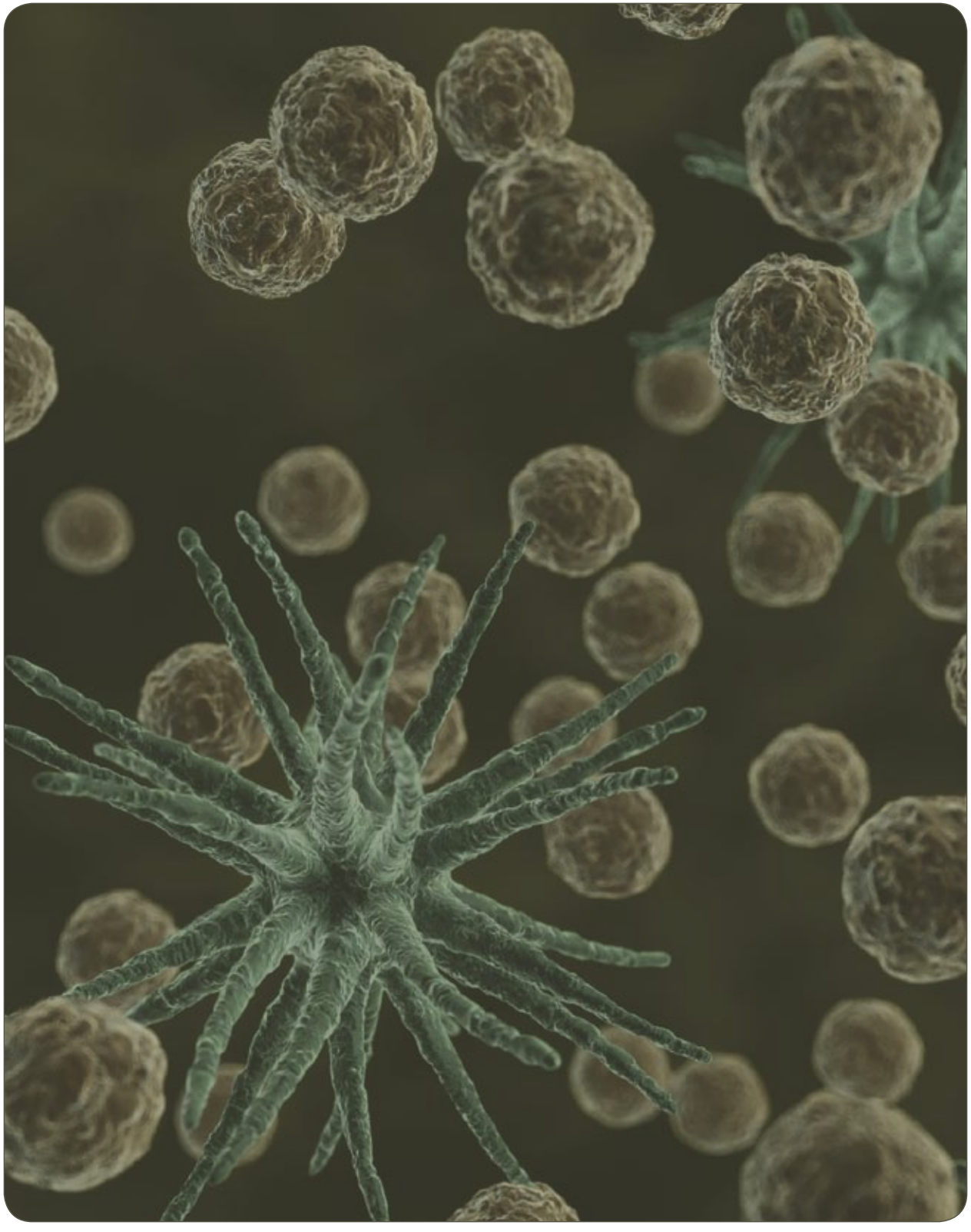
By their very nature, emerging technologies challenge our approaches to oversight and regulation. The novel properties exhibited by these technologies can underpin innovation in areas ranging from medicine to energy production, but can also present new risks and challenges to existing regulatory frameworks.

Along with nanotechnology, synthetic biology is a critical emerging technology that has gained the attention of both governments and the private sector. It builds upon the advances of biotechnology, applying the principles of engineering to the world of biology to finely tune existing organisms and even develop new ones from scratch. How this emerging science and its applications are developed and utilized by society will ultimately shape how it is regulated. Some scientists argue that synthetic biology is just a more powerful version of genetic engineering and thus does not need much in the way of new regulations. Though the first generation of synthetic biology-derived microorganisms is unlikely to be much different from those we have already seen, subsequent generations are likely to be much more complex displaying novel characteristics with little precedence in nature.

It would be easy to relegate discussions about oversight to the backburner. Procrastination bears a risk, however, since a productive dialogue may become more difficult as the technology matures and stakeholders become divided in their opinions about risks and benefits. One can start a discussion now with the basic question of whether existing regulations—for instance, the long-used Coordinated Framework for Biotechnology—will work with synthetic biology.

In this paper, Michael Rodemeyer of the University of Virginia provides an analysis of U.S. regulatory options for first-generation synthetic biology products. He examines the benefits and drawbacks of using the existing U.S. regulatory framework for biotechnology to cover products and processes enabled by synthetic biology. He finds that the similarities between biotechnology and synthetic biology are abundant enough to provide a good starting point, though how this emerging technology is framed for policymakers—as novel and potentially dangerous, or familiar and safe—will influence the makeup of any future regulatory policies.

David Rejeski
Director, Synthetic Biology Project
Director, Project on Emerging Nanotechnologies
Woodrow Wilson International Center for Scholars



Acknowledgments

Throughout my career, I've had the good fortune to work with outstanding scientists and engineers who have understood the importance of engaging policymakers on technical issues. Less frequently, I've had the opportunity to work with policymakers who likewise understand the need to engage with scientists and engineers. None of these former colleagues is likely to win the accolades of peers for trying to bridge the divide between physicist and novelist C.P. Snow's two cultures. But their willingness to do so may mark the difference between societies that can harness scientific knowledge and technological change for the benefit of all and those that perceive themselves to be resentful victims of technology's whims. To these envoys from both cultures we owe a great debt of appreciation.

Synthetic biology is the latest example of an emerging technology with remarkable promise to apply biology to societal needs, from renewable energy and environmental restoration to new drugs and diagnostic tools. Synthetic biology, like other powerful technologies, has also raised concerns, many of which have been raised by scientists themselves. The question now facing policymakers is how to ensure that the technology is developed in a way that maximizes benefits and minimizes risks, while allowing for change as new scientific knowledge is gained.

This report is an effort to look forward by looking back: applying some of the "lessons learned" about the regulation of biotechnology over the past 30 years to the emerging area of synthetic biology. It is by no means intended to be a comprehensive set of recommendations for the governance of synthetic biology, but rather a way to begin engaging the technical and policymaking communities in asking some of those questions.

I want to express my appreciation to the Synthetic Biology Project at the Woodrow Wilson International Center for Scholars for this opportunity to explore some of the governance questions associated with synthetic biology. I also benefited from the assistance of a number of legal scholars, regulatory experts and scientists to help me navigate some of the more complex shoals. I would particularly like to acknowledge the help of Jacqueline Corrigan-Curay, Mark Segal, Brent Erickson, Julia Moore, Robert Friedman, Michele Garfinkel, Fran Sharples, Anne-Marie Mazza, David Rejeski, Patrick Polischuk, Eleonore Pauwels and Andrew Maynard. I would also like to acknowledge those who reviewed earlier versions of this report and offered valuable comments, including J. Clarence (Terry) Davies, L. Val Giddings and Wendell Lim. While I owe my thanks to them for improving the report, the contents and opinions in the report are entirely my own and should not in any way be attributed to them or viewed as an endorsement. Similarly, any errors left remaining despite their assistance must be laid solely at my doorstep. Like the opinions expressed herein, any errors are entirely my own.

Michael Rodemeyer
Charlottesville, Virginia
March 2009

Executive Summary

Regulating New Technology: The Goldilocks Dilemma

The contribution of innovation and new technology to economic well-being has by now become so well established as to require little elaboration. Technology can create valuable and beneficial new products, increase efficiency and productivity and lower costs, all contributing to improved consumer welfare and economic growth. In recent years, new technologies in medicine, computers, communication and agriculture have revolutionized many industries and reshaped societies.

But in addition to benefits, new technologies can present new health or environmental risks that can pose difficult challenges for public policy. Regulators face the "Goldilocks dilemma": the need to get regulation "just right." If they are too precautionary, they will err by keeping safe, valuable new products off the market. If they are not precautionary enough, a product could come to market that could cause unacceptable harm.

The regulatory challenge is made all the more difficult because the information needed to assess risks of a new technology is often imperfect and uncertain, a not-surprising situation given its very novelty. In such cases, policymakers often look to previous experience in trying to determine how to address the risks and regulation of new technologies.

The discovery of gene-splicing biotechnology techniques in the mid-1970s is an example of a new technology that led to questions about appropriate regulation. Shortly after that breakthrough discovery, scientists raised concerns about the potential for harm that could result if microbes engineered through this new recombinant DNA (rDNA) splicing process were accidentally released from a laboratory. They feared that some harmful microorganisms could reproduce and spread, and the probability of such an outcome was at that point largely unknown. Scientists called for oversight by the National Institutes of Health to set standards to ensure that laboratory research was carried out in a manner that protected laboratory workers, the community and the environment. In the mid-1980s, as products began to be developed for use outside the laboratory, the Reagan administration developed a "Coordinated Framework" for the regulation of biotechnology products. The Coordinated Framework established the policy that biotechnology production processes posed no novel risks compared to conventional production processes and that risks should be therefore regulated under existing laws based on the risk characteristics of the final product, not the method by which it was made. As a result, in the United States, biotechnology products are regulated under the same laws that apply to comparable conventional products.

Synthetic Biology

Today, the next biotechnology revolution is brewing: synthetic biology. No longer limited to laborious gene-splicing from one organism to another, scientists are learning how to construct genetic code in the laboratory, with the hope of using synthetic genetic elements to build novel organisms that could be used for multiple purposes, such as manufacturing drugs or invading cancer cells in the body. While most commercial applications are likely to be years away, researchers today are working on synthetic microorganisms to produce the next generation of clean, renewable biofuels and of certain rare drugs.

Scientists have once again taken the lead in raising concerns about the risks of synthetic biology research. The issue that has garnered the most serious attention is the concern over

biosecurity—whether synthetic biology technology could assist bioterrorists in creating more dangerous pathogens. But today's scientists also face the same kind of biosafety concerns that were initially raised and subsequently addressed about the first genetically engineered microbes 35 years ago—the risks of harm to laboratory workers, the community and the environment should a harmful synthetic microbe be accidentally released and spread through the environment.

The initial framing of a new technology can have a strong impact on regulatory decisions. A new technology that is framed as being similar to an existing, familiar product reassures the public about its safety, allows policymakers to apply existing regulatory approaches and provides industry with a clear and predictable path to market. On the other hand, framing a new technology as being truly novel can raise public fears about its safety, pose a challenge for regulators and present an uncertain commercialization path for industry. Many scientists argue that synthetic biology is just a more powerful version of the genetic engineering that has been around for nearly 30 years and should therefore be treated in the same way.

This report examines that assumption as it applies to the likely first generation of synthetic biology products: synthetic microbes engineered to produce biofuels and drugs. The potential environmental and public health risks of a synthetic microorganism arise from two scenarios: an accidental release from a contained facility and an intentional release into a non-contained environment. These risks are similar in kind to the potential risks of microbes engineered through rDNA technology.

The first generation of synthetic biology microorganisms is unlikely to be remarkably different from or more complex than those created through other genetic engineering techniques, and will probably not pose difficulties in risk assessment. As the technology matures, however, it has the capability to produce complex organisms whose genomes have been assembled from a variety of sources, including artificial sequences designed and built in the laboratory. While the risk issues and risk assessment questions are similar to those raised by any genetically engineered organism, providing adequate answers to those questions may be significantly more difficult for such complex synthetic microorganisms.

The Challenge of Uncertainty

In rDNA biotechnology, regulators have typically evaluated the risks of genetically engineered microorganisms by comparing them to their well-known unmodified counterparts and understanding the function of the inserted genetic material. Regulators can compare the naturally occurring and genetically engineered varieties to ensure that the new organism is "as safe as" its known, conventional counterpart.

In complex organisms engineered through synthetic biology, however, it may be difficult to determine an organism's "genetic pedigree" if it has been assembled from multiple sources or contains artificial DNA. In addition, there is a question of whether the genetic sequences will continue to function as they did in their original sources, or whether there could be a synergistic reaction among the new components that leads to different functions or behavior. Scientists may be able to predict the functions of specific new genetic alterations based on growing understanding of comparable genetic components, but an organism assembled from genetic parts derived from synthetic or natural sources could display "emergent behavior" not seen in the original sources. The complexity of advanced synthetic microorganisms creates additional uncertainty in the ability to predict function from sequences and structures. Existing risk assessment methods may not prove adequate for predicting outcomes in complex adaptive systems. In addition, while many scientists believe that engineered organisms are unlikely to survive or reproduce in a natural environment, the capability of synthetic organisms to mutate and evolve raises questions about the potential of synthetic organisms to spread and to exchange genetic materials with other organisms if released into the environment. While these risks are again similar to those raised by any genetically engineered organism, it may be more

difficult to assess in advance the risk of complex synthetic organisms developed in the future.

Under such conditions of uncertainty, the challenge for regulators will be how to make decisions that neither over-regulate nor under-regulate. Risk research is an urgent requirement parallel to product development. While generic research will be useful, in many cases risk research must also be carried out in the context of specific organisms, products and intended applications.

Synthetic Biology Products Regulated Under Current Biotechnology Framework

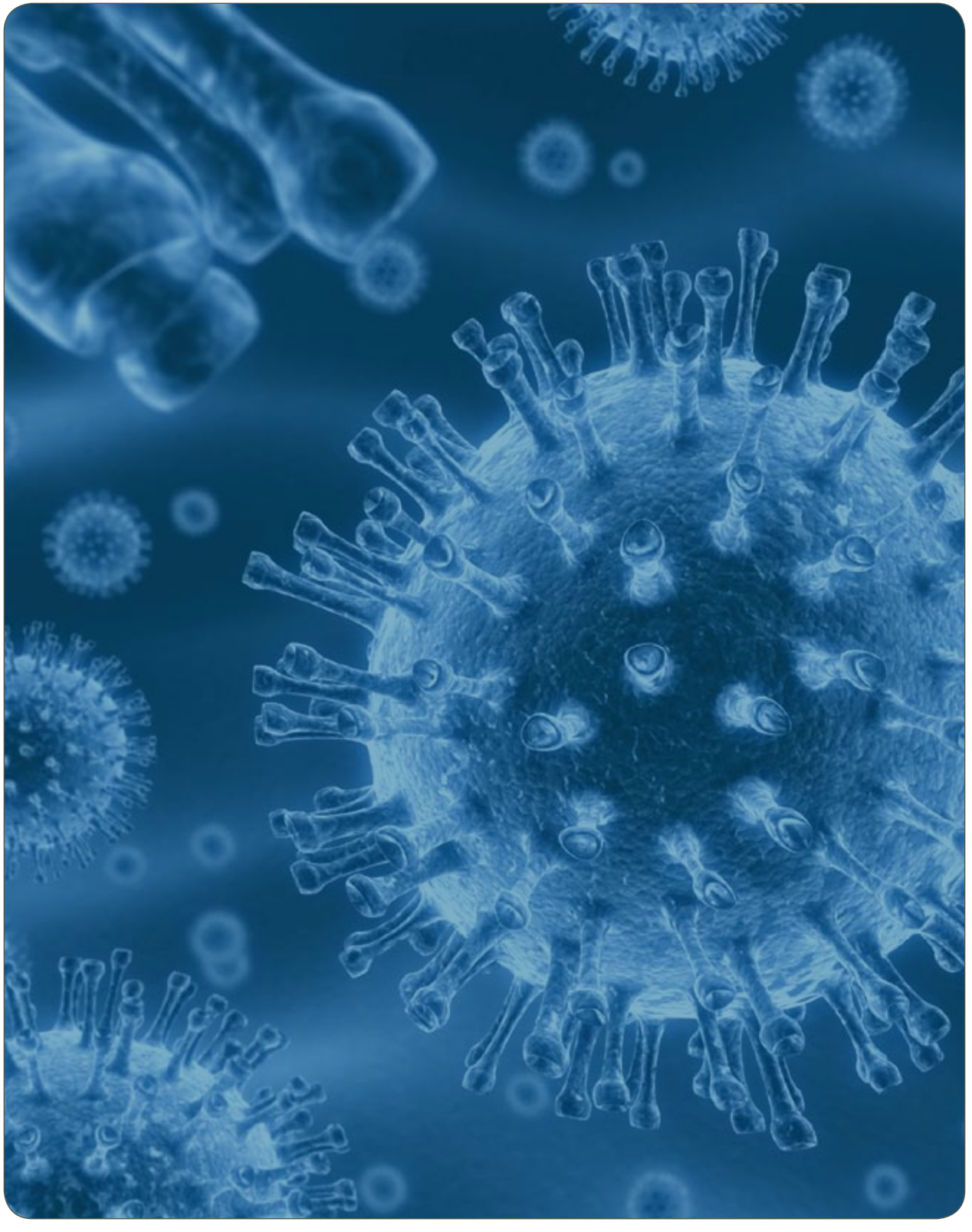
Most of the regulatory policies and guidelines originally adopted to address these risks for biotechnology appear to cover synthetic microorganisms in stages from research through commercialization, although there are some gaps and questions that agencies will need to address.

The National Institutes of Health (NIH) Guidelines for rDNA Research are the principal line of defense against the accidental release of a harmful genetically engineered organism from contained research laboratories. Assessing the potential risk of a proposed research activity and determining the appropriate level of confinement and biosafety procedures is at the heart of the NIH guideline-development process. In 2008, the NIH Recombinant DNA Advisory Committee (RAC) recommended revisions to the Guidelines to cover synthetic biology research and to provide clearer guidance to the research community on how to manage synthetic biology research, given the greater uncertainty involved with assessing its potential risks.

For commercial products, the existing regulatory framework for biotechnology is likely to cover most anticipated microbial products of synthetic biology, although agencies may need to modify some rules to clarify their intended application. The initial synthetic biology products are likely to be relatively simple modifications; however, as the technology matures, regulatory agencies will face challenges in assessing the potential risks of more complex synthetic organisms in order to determine appropriate biosafety controls. The greater uncertainty associated with the risk assessment of complex synthetic organisms will lead to different regulatory outcomes because of the regulatory patchwork that results from applying existing product laws. Depending on their nature, some products will require extensive testing and a pre-market regulatory safety approval, while others may go to market with considerably less testing and oversight. To use existing laws, a number of agencies have creatively stretched their authorities to cover biotechnology products, in ways that have generated criticism of both over- and under-regulation. In particular, some critics have argued that the Toxic Substances Control Act, which the Environmental Protection Agency would likely use to regulate synthetic microbes, is an inadequate regulatory approach for managing the risk of products of new technologies.

At the same time, while the process has not been without problems, the regulatory framework for biotechnology has generally been successful, particularly in comparison to the "process-oriented" regulatory approaches of Europe and other nations. Numerous valuable biotechnology products, both in biomedicine and in agriculture, have been successfully developed and commercialized throughout the United States and around the world, without any public health or environmental problems. U.S. consumers, particularly compared to their European counterparts, appear to have confidence in the regulatory system.

While the biotechnology regulatory model may well be the likely direction for the regulation of synthetic biology products, it is not a perfect match and carries with it some inherent problems. New legislation specifically for synthetic biology is an unlikely option, but some have urged Congress to rationalize and modernize the regulation of new converging technologies, instead of attempting to shoehorn each new area of technological development into laws previously written for a different set of issues.



I. Introduction: Biotechnology Past and Synthetic Biology Future

A. Introduction

Thirty-five years ago, Herb Boyer and Stanley Cohen discovered the principles of recombinant DNA (rDNA), or "gene splicing," technology, ushering in the era of modern biotechnology. Even as early researchers eagerly began to anticipate the potential applications of rDNA technology for medicine, agriculture and industry, some of them raised concerns about potential harm to public health and the environment should these newly created genetically engineered organisms be accidentally released from the laboratory and reproduce and spread in the environment.

The fact that a new technology was raising questions about risks—and appropriate policies to manage them—is hardly surprising. New technology often brings with it both promises and perils, and finding the right policies to maximize benefits while minimizing risks is not an easy task. New science and technology can challenge old paradigms and pose questions for which there are no clear answers. What was unique about the introduction of biotechnology, however, was that it was the scientists themselves who were raising the questions at the very early stages of their own research. From that beginning, policies to manage biotechnology's risks developed and evolved much as the science and technology itself. While biotechnology and its regulation have not always kept pace with each other or proceeded very smoothly, the system has, despite its flaws, largely worked: the past few decades have witnessed the introduction of numerous biotechnology-derived drugs, diagnostics and crops without apparent harm to the public health or the environment.

Today, advances in genetics, information technology and DNA synthesis are leading to the emergence of a new set of potentially far-reaching tools under the name of "synthetic biology." To some extent, synthetic biology is a logical extension of rDNA biotechnology. Instead of cutting and pasting discrete genetic materials from existing organisms, as with rDNA biotechnology techniques, researchers are increasingly able to design and build their own genetic materials from scratch in the laboratory and then to synthesize those artificial genetic constructs into novel organisms with engineered functions.

While synthetic biology mostly remains at the basic research stage, many believe that it will be at least as revolutionary as rDNA technology—and probably more so. Synthetic biology may be able to deliver on some of the as-yet unrealized hopes of biotechnology in terms of developing new drugs, diagnostics and environmentally friendly biofuels and other industrial chemicals.

As the process of turning science into technology begins in earnest, the issue of balancing benefits and risks is being raised again. As with the debate about early rDNA biotechnology, concerns have been raised about the potential risks to public health and the environment from accidental releases and from intentional non-contained uses. In addition, synthetic biology has raised serious concerns about biosecurity: the potential of the technology to enhance the ability of bioterrorists to develop more virulent pathogens. Some in the scientific community have once again taken the lead in calling for self-governance (Church, 2005). In addition, some non-governmental organizations have urged caution and pushed for formal oversight of synthetic biology (ETC Group, 2007).

Are the U.S. regulatory policies for rDNA biotechnology products developed over the past 25 years an appropriate template for first-generation synthetic biology products? To what extent does the existing regulatory framework developed for biotechnology products adequately address concerns about potential risks from accidental or intentional releases of synthetic organisms?

B. Biotechnology Past: The Development of Regulatory Policies for Products of rDNA Biotechnology

The history of the development of a regulatory framework for rDNA biotechnology has strong relevance for issues concerning the governance of synthetic biology. In 1974, only a short time after Cohen and Boyer's discovery, several leading molecular biologists raised concerns about the safety of rDNA research and called for a moratorium on certain research until safety guidelines could be developed and more experience gained to assess risk (Berg, et al., 1974). Meeting in Asilomar, California, in 1975, the molecular biologists called for the development of safety guidelines and a process for reviewing the safety of proposed rDNA experiments (Berg, Baltimore, Brenner, Roblin III, & Singer, 1975). These recommendations led to the establishment of the Recombinant DNA Advisory Committee (RAC) at the National Institutes of Health (NIH) to oversee the safety of rDNA research and to define appropriate standards for containment of potentially risky research.

As the first commercial products intended for non-contained use in the environment began to emerge from laboratories in the mid-1980s, federal regulators charged with responsibility for protecting public health and the environment grappled with applying existing laws to new biotechnology products. In 1986, the White House Office of Science and Technology Policy published a "Coordinated Framework" for the regulation of biotechnology (51 Fed. Reg. 23302 [1986]). That policy statement, which remains the basic guidance document for U.S. biotechnology policy, established a number of key principles. The Coordinated Framework, reflecting scientific consensus, stated that recombinant DNA technology did not present any unique risks or pose any specific problems that were different than those of conventionally produced organisms. As a result, the focus of government regulation should be the risk characteristics of the final product, not the process by which it was made. Looking at the existing regulatory authority, the policy statement further concluded that then-existing laws were adequate to deal with the potential risks associated with any biotechnology-derived product likely to be developed in the foreseeable future.

As a consequence, since the mid-1980s, biotechnology products developed in the United States have been reviewed under the same sets of laws and regulations that apply to conventionally produced products (Tables 1-3). This technology-neutral approach means that the type of regulatory review depends on the specific category of the product. For example, the Food and Drug Administration (FDA) regulates food, feed

TABLE 1. FEDERAL LAWS POTENTIALLY APPLICABLE TO GE ORGANISMS AND PRODUCTS DERIVED FROM THEM

Title of Act	Abbreviation	Agency	Cite
The Federal Insecticide, Fungicide, and Rodenticide Act	FIFRA	EPA	7 USC § 136
The Toxic Substances Control Act	TSCA	EPA	15 USC § 2601
The Food, Drug, and Cosmetic Act	FDCA	FDA; EPA	21 USC § 301
The Plant Protection Act	PPA	USDA	7 USC § 7701
The Virus Serum Toxin Act	VSTA	USDA	21 USC § 151
The Animal Health Protection Act	AHPA	USDA	7 USC § 8031
The Federal Meat Inspection Act	FMIA	USDA	21 USC § 601
The Poultry Products Inspection Act	PPIA	USDA	21 USC § 451
The Egg Products Inspection Act	EPIA	USDA	21 USC § 1031
The Animal Damage Control Act	ADCA	USDA	7 USC § 426
The Animal Welfare Act	AWA	USDA	7 USC § 2131
The National Environmental Protection Act	NEPA	(All)	42 USC § 4321

Source: Pew Initiative on Food and Biotechnology (2004).

and food additives, as well as human and animal drugs, biologics and medical devices. The Environmental Protection Agency (EPA) regulates pesticides, pesticide residues in food and certain "new chemical substances." The U.S. Department of Agriculture (USDA) regulates potential animal and plant pests under various laws. Since each agency operates under different laws and regulations, the type of regulatory review that a product will receive differs dramatically. For example, drugs and pesticides cannot be marketed until the regulatory agency has found that the products are "safe," and the burden of proof is on the developer. (The definition of "safety" also changes from law to law.) On the other hand, new, conventionally bred whole-food varieties may be introduced to the market without any prior regulatory review; the food manufacturer is responsible for ensuring the safety of food. While biotechnology products are regulated under these general authorities, each agency has had to interpret and apply these laws to biotechnology products through regulations and guidance.

Even after more than 20 years, the regulatory framework for rDNA biotechnology products continues to evolve[1] and generate controversy. Some critics have argued that the biotechnology regulatory system is inadequate to address the range of potential risks posed by various biotechnology products (see, e.g., McGarity, 2002; Bratspies, 2004), while others argue that biotechnology is heavily overregulated (see, e.g., Miller & Conko, 2005; McHughen, 2007; Strauss, 2003).

Despite these continuing debates, the regulatory system for biotechnology has generally worked as intended. Useful and valuable new products developed through rDNA biotechnology have come to the market. Recombinant DNA biotechnology has revolutionized the development of new drugs, therapies and medical diagnostics. An estimated 200 new therapies and vaccines have been developed through biotechnology, with hundreds more in clinical testing (Biotechnology Industry Organization, 2008). In agriculture, companies have developed new varieties of pest-resistant and herbicide-tolerant corn, soybeans, cotton and canola that have been rapidly adopted by U.S. and Canadian farmers (U.S. Department of Agriculture, National Agricultural Statistics Service, 2008). In 2006, publicly traded U.S. biotech companies were estimated to have generated nearly $59 billion in revenues (Biotechnology Industry Organization, 2008).

During this period, the biosafety record of new biotechnology products has been reassuring. Certainly, the major fears that were expressed in the early stages of the technology have not come to pass.[2] Whether that result is because scientists and industry have been cautious, because regulators have done a good job in keeping risky products

TABLE 2. FEDERAL LAWS POTENTIALLY APPLICABLE TO GE ORGANISMS AND PRODUCTS DERIVED FROM THEM
(uncertain areas in italics)

Genetically Engineered Organism	Ageny	Law
PLANTS		
All Plants	USDA-APHIS	PPA
ANIMALS		
Animals (including fish)	*FDA*	*FDCA*
Livestock	*USDA*	*AHPA; ADCA*
MICROORGANISMS	EPA; USDA	TSCA; PPA

TABLE 3. THE REGULATION OF PRODUCTS DERIVED FROM GENETICALLY ENGINEERED ORGANISMS
(uncertain areas in italics)

Genetically Engineered Organism	Ageny	Law
HUMAN FOODS		
Whole Foods		
Plants (i.e., vegetables, fruits)	FDA-CFSAN	FDCA
Meat, Poultry, and eggs	USDA-FSIS	FMIA; PPIA; EPIA
	FDA-CVM	*FDCA*
Fish	FDA-CVM	FDCA
Food Articles		
Food additives	FDA-CFSAN	FDCA
Dietary supplements	FDA-CFSAN	FDCA
HUMAN FOODS	FDA-CVM	FDCA
DRUGS AND BIOLOGICS		
Human drugs	FDA-CDER	FDCA
Human biologics	FDA-CBER	FDCA
Animal drugs	FDA-CVM	FDCA
Animal biologics	USDA-APHIS	VSTA
HIGH-VALUE PRODUCTS		
Cosmetics	FDA-CFSAN	FDCA

Source: Pew Initiative on Food and Biotechnology (2004).

"Federal regulators charged with responsibility for protecting public health and the environment grappled with applying existing laws to new biotechnology products."

off the market or because of simple good fortune, remains a debatable question. In the absence of perceived food- or drug-safety problems, many U.S. consumers remain unaware of the ubiquity of biotechnology products (PIFB, 2006). Whatever the reasons, the U.S. public has acquiesced in the introduction of biotechnology products and appears to trust the regulatory system to ensure safety. A more difficult question is whether the regulatory system has had the effect of keeping safe and useful products off the market by raising regulatory and economic barriers to entry, as some have argued (Miller & Conko, 2005).

That is not to say that the regulation of biotechnology, particularly in the area of agriculture and food, has been without problems in the United States.[3] But U.S. regulation has been straightforward by comparison with that in other parts of the world, especially Europe, where popular opposition to genetically engineered food and crops remains strong. The reasons for European rejection of genetically engineered foods are complex (Jasanoff, 2005), but one major factor unquestionably is the "mad cow" food crisis in the mid-1990s, which shook consumer confidence in the safety of the food supply and created distrust of the governments that had been consistently assuring the public that beef was safe to eat. For a number of reasons, politicians in the European Union (E.U.), reflecting European public opinion, have been reluctant to approve genetically engineered foods and crops, despite general scientific agreement that they are likely to be substantially equivalent to their conventionally produced counterparts. E.U. policy, in direct contrast with U.S. policy, more stringently regulates genetically engineered crops and foods under specific new laws and requires mandatory labeling. As a consequence of regulation and consumer opinion, few genetically engineered crops and foods have been approved and even fewer are offered for sale in the market. This policy conflict has led to trade disputes and unquestionably slowed the global introduction of agricultural biotechnology.

Could the same divergence pattern emerge with synthetic biology? Early analyses of press coverage of synthetic biology in the United States and the European Union have shown a more "precautionary" framing in Europe with a focus on a much wider range of potential risks (Pauwels & Ifrim, 2008). For example, U.S. news stories were more likely than European news stories to focus on potential benefits of synthetic biology.

C. Synthetic Biology Future: The Relevance of Biotechnology Regulation to Synthetic Biology

In many ways, the current status of synthetic biology can be roughly compared to the situation facing molecular biologists in the mid-1970s. Synthetic biology remains a loosely confederated set of technologies and disciplines, although its potential power has been amply demonstrated. Much of the ongoing work is at the fundamental research level, as scientists continue to try to understand how to design synthetic genetic constructs and to synthesize larger sequences of DNA. How quickly this science will advance is difficult to predict. Designing synthetic microorganisms may turn out to be much more difficult than anticipated (Aldrich, Newcomb, & Carlson, 2008). On the other hand, given the recent history of unexpected developments in the biological sciences, it is possible that progress could be quite rapid and that products could be heading to the marketplace in the not-too-distant future.

Given the status of synthetic biology, are the policies and approaches developed over the past two decades to address similar concerns about rDNA technology appropriate to apply to synthetic biology research and commercialization? To what degree, if any, do the guidelines and regulations developed for rDNA technology apply to synthetic biology research and commercialization?

In examining those questions, this report will focus primarily on the potential risks to the public health and the environment of an accidental release of a harmful synthetic microorganism, and on the health and environmental impacts of synthetic microorganisms intended for non-contained uses in the environment—the same concerns expressed in the early development of rDNA biotechnology. To be sure, synthetic biology raises other significant concerns. The issue of biosecurity has already received significant debate, particularly in the academic and defense communities. It is not the intent of this report to revisit those issues (National Science Advisory Board for Biosecurity, 2006; National Research Council, 2004; Garfinkel, Endy, Epstein, & Friedman, 2007). Synthetic biology also raises significant ethical, religious and social impact issues (Balmer & Martin, 2008). When the first reproducing synthetic organism is created at some point in the future, it will inevitably rekindle the controversy over the propriety of "creating life" previously raised by some rDNA biotechnology applications. Issues relating to patents and intellectual property are also likely to be controversial and complex. While all these issues are clearly significant and will have major implications for the future trajectory of synthetic biology, they are beyond the scope of this study.

"…given the recent history of unexpected developments in the biological sciences, it is possible that progress could be quite rapid and that products could be heading to the marketplace in the not-too-distant future."

II. Synthetic Biology—Definitions, Applications and Risks

A. What Is Synthetic Biology?

Synthetic biology is a set of tools and approaches that is emerging from the convergence of advances in molecular biology, genomics, information technology and engineering. As scientists have sequenced the genomes of humans and other organisms, they have begun to decipher more of the functions of genes and other genetic components that regulate gene expression, such as signaling and switching. As scientists learn how to "read" these discrete genetic units and understand how they function within and across organisms, they have begun to construct genetic units from scratch using chemicals in the laboratory and DNA synthesizers that enable them to "write" whatever DNA sequence they care to design. The rise of commercial DNA synthesis companies enables scientists to specify the DNA sequence they want, order it over the Internet and have it delivered. The cost of commercial DNA synthesis has dropped 700-fold over the last decade, reducing the costs of gene synthesis from about $30 per base pair to less than $1 a base pair (Newcomb, Carlson, & Aldrich, 2006). The decreasing cost and increasing accuracy of commercial gene synthesis enables scientists to design genetic sequences from scratch rather than try to arduously recombine them from natural sources.[4]

In a sense, synthetic biology is engineering applied to molecular biology. From an engineering perspective, the genetic "code" is analogous to computer code—it is information that can be read and written, compiled and executed to carry out functions. As the Web site of one synthetic biology company states, "[W]e view the genome of the cell as the operating system and the cytoplasm of the cell as the hardware" (www.syntheticgenomics.com/science.htm). Similarly, genetic sequences that control and regulate gene expression are viewed as analogous to switches, circuits and other functional segments of an engineered system.

In general, the goal of synthetic biology is to design, engineer and build functional organisms by assembling discrete parts of natural and synthetic genetic material. The purposes for which scientists are using synthetic biology can be roughly divided into two categories. In the first category, scientists are using synthetic biology as a research tool to better understand the underlying "natural" biology. These efforts have been characterized as "deconstructing life"—taking it apart, trying to figure out the pieces and then putting them together again to see whether the assumptions about the functions of the parts are correct (Lorenzo, Serrano, & Valencia, 2006). Synthesizing a functional organism from parts is a way to test and validate fundamental understanding of biological systems and their evolution. This process is similar to the way in which scientists have used recombinant DNA technology to "knock out" a gene in research animals in order to determine the function of that gene.

Other scientists are more interested in "constructing life": using synthetic biology to assemble genetic pieces in an effort to make altogether-new, functional organisms. The goal is to understand general design principles, regardless of their relationship to natural biology, that can then be used in the construction of synthetic organisms that do not exist in nature. For example, some scientists are looking for interchangeable genetic parts that might be tested, validated as building units and reassembled to create functional devices. While the parts come from biological systems, their design and assembly are entirely synthetic (Benner & Sismour, 2005; Endy, 2005).

At this point, synthetic biology is more of a collection of tools and technologies than it is a specific discipline with a unified purpose. Various efforts have been made to come up with a consensus definition of

synthetic biology that covers all the activities currently being carried out under that title. The Royal Society has defined it as "an emerging area of research that can broadly be described as the design and construction of novel artificial biological pathways, organisms or devices, or the redesign of existing natural biological systems" (The Royal Society, 2008). One writer attempted to summarize it as "the area of intersection of biology and engineering that is focused on the design and fabrication of biological components and systems that do not already exist in the natural world, and the redesign and fabrication of existing biological systems" (Bhutkar, 2005). One group summed up the variety of activities with the observation that "synthetic biology is the engineering of biology: the synthesis of complex, biologically based (or inspired) systems, which display functions that do not exist in nature. This engineering perspective may be applied at all levels of the hierarchy of biological structures—from individual molecules to whole cells, tissues and organisms. In essence, synthetic biology will enable the design of "biological systems" in a rational and systematic way" (European Commission, 2005).

Perhaps a better way to understand the emerging discipline of synthetic biology is to look at some examples of current research. Craig Venter, the scientist who raced the government-sponsored Human Genome Project with a novel sequencing method, is leading several research initiatives. At the Institute for Genomic Research (now part of the J. Craig Venter Institute), researchers have become interested in determining the minimal set of genes required to support "life." Working with the *M. genitalium* bacterium, an organism with one of the smallest genomes consisting of only 517 genes, researchers were able to reduce the number of genes to a core set of between 265 to 350 genes that still enabled the bacterium to sustain life. Beyond its purpose in helping understand the functions of genes, part of the motivation for this research is the concept of creating a small, flexible and universal bacterial "platform" that could be modified with different gene packages to carry out different functions—such as producing drugs or industrial chemicals.

Efforts to build whole-length genomes from scratch, using genomic-sequence information, have been going on for some time. In 2002, a team of researchers made headlines for assembling an infectious poliovirus directly from nucleic acids in the laboratory (Cello, Paul, & Wimmer, 2002). In the following year, researchers at the Venter Institute succeeded in constructing the genome of a similar-length virus in only two weeks—in contrast to the year it took to assemble the poliovirus (Smith, Hutchinson III, Pfannkoch, & Venter, 2003). In 2005, scientists reconstructed the genome of the 1918 strain of influenza flu virus, using samples of DNA taken from frozen cells of victims to generate a genetic sequence to copy (Tumpey, et al., 2005). These studies launched a significant debate about the biosecurity implications of sequencing and synthesizing infectious and pathogenic agents.

More recently, in February 2008, researchers at the Venter Institute announced the largest synthesized whole genome to date—the nearly 600,000 base-pair-long genome of *M. genitalium*. Evidencing the continuing acceleration of genetic sequencing and synthesizing technologies, the *M. genitalium* genome was an order of magnitude larger than any previously synthesized DNA product (Casci, 2008).

An example of the "construction" category of synthetic biology is provided by Drew Endy (now at Stanford) and his former colleagues at the Massachusetts Institute of Technology (MIT), who have established the Biobricks Foundation (http://bbf.openwetware.org/), a non-profit organization that is attempting to create an open catalog of standardized DNA parts that encode basic biological functions, such as a switch that turns gene expression on or off. Based on the open-source software philosophy, these BioBrick parts are made freely available for researchers around the world. Each year, the foundation supports the International Genetically Engineered Machine competition in which undergraduate student teams compete to construct novel biological machines using BioBrick standard parts (www.2008.igem.org). In 2007, entries included bacteria that mimic the behavior and property of red blood cells, "infector detector" organisms that detected antibiotic resistant microbes and a bacterial-based photographic imaging system (Lichtenstein, 2007).

Other research that comes under the umbrella of synthetic biology includes efforts to create synthetic DNA—DNA that is not limited to the naturally occurring base pair combinations of A-T, G-C. Expanding the genetic "alphabet" by creating novel chemical base pairs could be useful for any number

of purposes, including the potential to penetrate cell wells and neutralize undesirable RNA molecules (Pollack, 2001; Geddes, 2008). Scientists have already developed diagnostic tests that use artificial nucleotides to screen for HIV, cystic fibrosis and other diseases (Benner, 2004). Other efforts are focusing not just on genetic sequences but on whole "proto-cells" that would create synthetic living cells (Szostak, Bartel, & Luisi, 2001; O'Malley, Powell, Davies, & Calvert, 2007).

How does synthetic biology differ from rDNA biotechnology? To some extent, synthetic biology is an extension of biotechnology; there is a certain amount of overlap, and no clear defining line between the two areas.[5] For example, molecular biology and rDNA techniques can also be used to alter genetic sequences. However, DNA synthesis technologies provide a much more efficient way to achieve the same ends, permitting scientists to focus on novel designs unlimited by natural constraints. As one study explained, "Whereas other recombinant DNA methods start with an organism's genome and modify it in various ways, with results that are constrained by the original template, synthetic genomics permits the construction of any specified DNA sequence, enabling the synthesis of genes for entire genomes" (Garfinkel, Endy, Epstein, & Friedman, 2007).

Because synthetic biology is not limited to using existing organisms, synthetic biology allows more complex and sophisticated engineering than can be achieved through recombinant DNA techniques. Current biotechnology techniques generally focus on modifying components of living cells to achieve a desired function, such as splicing a gene from one organism to another, or forcing a mutation in a gene for a specific purpose. In contrast, "synthetic biology is concerned with designing and building artificial regulatory elements into genomes or constructing a complete genome from scratch" (Bhutkar, 2005). As Jay Keasling of the University of California at Berkeley, explains, "We're talking about taking biology and building it for a specific purpose, rather than taking existing biology and adapting it. We don't have to rely on what nature's necessarily created" (Pollack, 2006).

B. Potential Applications

Despite these scientific breakthroughs, synthetic biology for the most part remains at the basic research stage. Most of the funding for synthetic biology work comes from the public sector, although venture capital appears to be slowly increasing, particularly in the area of biofuels, discussed in more detail below (International Risk Governance Council, 2008; Aldrich, Newcomb, & Carlson, 2008). With some of the exceptions noted below, most observers do not expect commercial applications to arise from synthetic biology for another decade. However, as is always the case with technology, unforeseen breakthroughs could enable more rapid technology development than currently expected. Given the current state of the science, several observers have suggested that it is "quite conceivable that in 10 years we will be able to fully redesign or make new cells, bacteria or viruses" (Serrano, 2007). Craig Venter in 2004 predicted that engineered cells and life forms would be relatively common within a decade (Ferber, 2004). Nevertheless, many significant technical hurdles remain (Holt, 2008).

While the time horizons may be uncertain, researchers envision an astonishing array of potential synthetic biology applications: more efficient production of vaccines for human and animal health and related diagnostics, new and improved drugs, bio-based manufacturing, sustainable energy production from renewable sources and bioremediation of environmental contamination (Pieper & Reineke, 2000) and biosensors capable of detecting toxic chemicals (International Risk Governance Council, 2008). While similar goals are being pursued using conventional technologies, synthetic biology offers several potential advantages. Synthetic microorganisms might be capable of producing pharmaceutical or industrial compounds that would be very difficult to produce using existing chemical or biological techniques. Further down the line, synthetic biology may

even be able to create molecular-sized tools for tissue repair and cell regeneration (European Commission, 2005). Scientists at the California Institute of Technology are working on synthetic biological switches that would reside within a cell and detect and destroy cancer (Pollack, 2006). Synthetic biology may enable public health officials to quickly design and produce synthetic vaccines in order to respond to rapidly evolving viruses (Garfinkel, Endy, Epstein, & Friedman, 2007). Ari Patrinos of Synthetic Genomics has talked about using synthetic genomics to find the "holy grail": microbes that would convert carbon dioxide into a feedstock for biofuels and biochemicals (Patrinos, 2008).

1. Biofuels

While most of these applications remain in an indefinite future, many believe that the first potential application (the "killer app") of synthetic biology may well be in the area of biofuels (Wade, 2007). Biofuels come from renewable resources that can be grown in the United States and have the potential to be carbon-neutral, thereby serving the twin policy goals of reducing dependence on imported oil and reducing the carbon impact of fossil fuels. Given high energy prices, the environmental and economic limitations of producing ethanol from corn and significantly increased public and private funding for R&D of alternative fuel sources, researchers are ramping up efforts to use synthetic biology to create biofuels.

One area of research interest is the development of alternative and improved feedstocks—such as switchgrass and other cellulosic biomass—to produce biofuel. The major technical limitation with such feedstocks is that they typically have dense cell structures that must be broken down to yield the sugars from which biofuels are made—a process that is in itself energy intensive. To make the biofuel process more energy efficient, and therefore more economical and environmentally sustainable, scientists are using biotechnology and synthetic biology tools to look at several points in the biofuel process where biology could make a significant difference. One area of interest is in developing a microbe with the ability to both extract the sugars from cellulosic biomass and to convert those sugars to fuel, consolidating the separate biological processes and thereby reducing the costs of extraction (Lynd, van Zyl, McBride, & Laser, 2005).

The most advanced use of synthetic biology to create biofuels, however, has been in the development of synthetic microbes that can more efficiently convert sugars directly to fuels that are directly compatible with the range of fuels currently used (i.e., gasoline, diesel, jet fuel). Several companies have small-scale pilot projects that have demonstrated technical feasibility, but scaling up to produce industrial quantities of biofuels at a competitive price remains a significant challenge.

While it is difficult to say how close any of these products may be to being commercialized, at least a half-dozen companies are developing products in this area, and several claim to have products or processes that are close to testing on larger scales. Whether all of these microorganisms can be considered products of synthetic biology or simply advanced biotechnology is not always clear; for the most part, the companies listed below have claimed that they are using synthetic biology techniques. A non-exhaustive illustrative list of these companies' activities are noted below.

LS9 (www.ls9.com), a company located in South San Francisco and founded by Harvard Medical School professor of genetics George Church, is developing a proprietary microbe through synthetic biology to enable the development of a variety of products that will be directly comparable to existing fuels derived from oil, such as gasoline, diesel and jet fuel. Starting with feedstocks such as sugarcane and cellulosic biomass, these synthetic organisms convert sugars directly into hydrocarbons more efficiently than current methods. In September, 2008, LS9 opened a pilot plant to test this technology with the goal of a constructing a 50,000- to 100,000-gallon production facility by 2011 to produce a replacement for diesel fuel.

Amyris (www.amyris.com) is a California startup company using synthetic biology to develop engineered microbes to produce high-value compounds, including renewable biofuels. Like LS9, Amyris is looking to use its proprietary microbes to produce diesel from sugarcane stock. According to Amyris, the new biofuel process should achieve lower costs and greater scale than vegetable oil-based biodiesel. In 2008, Amyris signed an agreement with Crystalsev, one of Brazil's largest ethanol distributors and marketers, to begin scaling up for commercialization in 2010. The joint project

predicts being able to produce 30 million gallons of diesel as early as 2010, with gasoline and jet fuel production following within one to two years.

OPX Biotechnologies (www.opxbiotechnologies.com), located in Boulder Colorado, uses synthetic biology to design custom organisms in biofuel production to reduce production costs. In addition to its engineering capability, OPX is using a search technology platform to scan genomes and identify potentially useful gene sequences, enabling the testing and engineering of microbes 1,000 to 5,000 times faster than conventional methods, according to the company. The company states, "Our ability to understand rapidly the workings of microbes at the individual gene level and test a huge number of modifications simultaneously enables us to engineer new microbes that can provide major improvements in tolerance, productivity, and specificity for fuel and chemical production."

Solazyme (www.solazyme.com), another South San Francisco firm, is using a patented process to make biodiesel from genetically modified marine algae. The fuel, named Soladiesel, is being road-tested in California, and the company expects to be producing commercial quantities in several years. Solazyme is also working on other synthetic biology applications. The company promotes its expertise in automated directed evolution (i.e., screening mutated organisms for desirable functions), optimizing production strains and metabolic engineering.

Gevo (www.gevo.com), located in Denver, has the goal of developing new cellulase genes, testing them in mixtures of enzymes and then engineering those genes into bacteria that will efficiently convert sugars into butanol and isobutanol at costs comparable to those of current ethanol production.

Synthetic Genomics (www.syntheticgenomics.com), founded by Craig Venter, may have the most ambitious R&D plans. The company is pursuing paths similar to those of the companies above, searching for and engineering microorganisms that directly convert feedstocks (such as sugar and cellulose) into biofuels. The company recently predicted that a pilot-scale project for liquid biofuels would be operating within two years, with large-scale production by 2013. In addition, Synthetic Genomics is looking more broadly at the renewable-fuel process, including the genetic modification of feedstocks to increase yields in sugars and oils and potentially enhancing soil microbes to improve feedstock performance (Patrinos, 2008). In addition, the company has partnered with BP to use synthetic genomics for enhancing the biological conversion processes for subsurface fossil fuels, such as oil shale, natural gas, oil and coal.

2. Pharmaceuticals

Just as genetic engineers used the tools of recombinant DNA to develop engineered bacteria to produce insulin and other valuable drugs and chemicals, scientists are using the more advanced tool set of synthetic biology for the same purposes. The high value of biopharmaceuticals makes this area attractive both to venture capital investors and to philanthropic foundations like the Bill & Melinda Gates Foundation. At this early stage of research, most of the work is being done at universities and university-based startup companies, rather than at large pharmaceutical companies.

One area of research involves engineering the metabolic pathways of microorganisms to dramatically increase the production of terpenoids, a class of molecules with wide-ranging pharmaceutical applications, including anti-cancer and anti-malarial properties (Ajikumar, Tyo, Carlsen, Mucha, Phon, & Stephanopoulos, 2008). Jay Keasling, at the University of California, Berkeley, published work in 2006 demonstrating the modification of a yeast to produce artemisinic acid, a precursor of artemisinin, a highly effective drug against malaria (Ro et al., 2006). Artemisinin is currently derived from the sweet woodworm plant, but is expensive and in short supply.[6] Keasling's process is being further developed to optimize yield and increase scale of production by Amyris, the California synthetic biology company with which Keasling is associated. Amyris, which is being supported in this effort by the Bill &Melinda Gates Foundation, has indicated that it will take no profits from this technology. (Keasling is using a similar platform in his for-profit biofuel work.) In March 2008, Amyris announced that it had partnered with the Institute for OneWorld Health, a U.S.-based non-profit pharmaceutical company, and the pharmaceutical company Sanofi-Aventis, for the development and commercialization of synthetic artemisinin, if they can achieve certain technological benchmarks.

III. Policies and Options: Managing the Risks of New Technologies

A. Policy Goals and Framing New Technologies

As illustrated by the history of rDNA biotechnology, new technology often presents new challenges for policymakers. Policymakers often have to balance competing policy goals in responding to new technologies. One of the fundamental goals of U.S. policy is to encourage the development of products that bring valuable new benefits to society. A variety of policy tools provide incentives for the development of new technologies, including tax policies and intellectual property policies.[7] To promote these policy goals, policies also seek to ensure that there is a level playing ground for competition and some certainty in the pathway to commercialization for industry.

In that regard, policymakers often look to existing laws and regulations for guidance in developing approaches to new technologies. How should the new technology be treated compared to existing and established technologies? For example, as new technologies have created new forms of communication, policymakers have struggled to respond. In the 1950s, policymakers grappled with applying the rules of radio broadcasting to television. As cable companies arose to compete with broadcasters, policymakers had to issue new rules for competition and content regulation. And as the Internet has ushered in whole new forms of communication, policymakers have struggled to figure out whether it should be treated like newspapers, broadcasters, telephone companies, cable companies or something else entirely. Decisions made by policymakers can have profound impacts on competition and innovation—a fact not altogether lost on companies and their lobbyists.

The initial framing of a new technology in reference to existing technologies can have important policy implications. In the 1970s, for example, the assembly of molecular biologists at Asilomar implied (perhaps unintentionally) that rDNA technology was something fundamentally new and different from existing biological techniques. But by the 1980s, many molecular biologists, the biotech industry and ultimately government policymakers in the United States were emphasizing that biotechnology was only a logical extension of conventional breeding techniques and therefore could be regulated under existing laws and approaches (Jasanoff, 2005). That decision provided developers with an established and understood regulatory pathway for product commercialization. In contrast, European activists were more successful in framing biotechnology as a radically new and potentially risky technology that required special regulatory scrutiny. Political pressure brought about in part by strong anti-biotechnology European public sentiment led to policy delays and more stringent process-based regulations. Those different perspectives on biotechnology have had profound economic implications on trade and on the development and adoption of agricultural biotechnology.

Similar framing issues about the relative safety or risk of a new product can affect the regulatory environment. Over the years, U.S. policymakers have developed very different regulatory approaches for classes of products based on their perceived risk. Most novel products are not subject to any legally mandatory pre-market regulatory review for safety, although manufacturers are responsible for ensuring that their products are safe under various statutory laws and under common law.[8] If safety or health problems arise, regulatory agencies have the authority to respond. But other classes of products—such as new drugs, pesticides and food additives—are perceived as being potentially harmful to the public health or the environment and therefore may not

be sold until the appropriate regulatory agency has found that they are safe, based on evidence submitted by the developer.

Whether a new technology is framed as presumptively risky or safe has significant implications, not only for the protection of public health and the environment but also for its commercialization. Laws and regulations that require a mandatory pre-market safety-approval process may provide a higher level of protection and precaution, but at the cost of an expensive, lengthy and often-uncertain regulatory process. Typically, the developer needs to provide the agency with the information it needs to determine that the product is safe. That may involve years of testing to meet strict agency protocols for addressing various concerns. As a consequence, mandatory pre-market approval approaches create a fairly high barrier to entry to new products, thereby conflicting with the policy goal of encouraging the introduction of valuable new products to the marketplace. This conflict is particularly apparent in the cases where a new technology, though not without some risk, appears to be significantly safer than a product already on the market. (At the same time, having regulatory approval provides an economic benefit to the developer by helping ensure market and consumer confidence in the safety of the new product.)

On the other hand, allowing a new technology to come to market more quickly, without a pre-market safety-approval process, increases the chance that some harmful product will be missed by regulators. Balancing the conflict between these two policy goals—protecting public health and the environment on the one hand and encouraging valuable and innovative new products on the other—is a well-recognized challenge. The history of FDA drug regulation provides ample examples where the FDA has been roundly criticized for dragging its heels in approving helpful new drugs in some years, and then pilloried for recklessly approving dangerous drugs in other years. Policymakers need to balance the desire to avoid over-regulation on one hand—that is, keeping truly beneficial safe products off the market—with a desire not to under-regulate—that is, allowing a truly harmful product onto the market. This is the traditional "Goldilocks dilemma": determining how to impose only those regulatory controls and costs that are necessary to match the actual risks of a product.

When they have the legal flexibility to do so, regulators often turn to the process of risk assessment to help them determine the potential risk of novel products and new technologies and to tailor appropriate risk management controls. While risk assessment in theory provides an approach with the potential for a more nuanced and tailored approach to risk management, it suffers from several limitations. As noted in more detail below, risk assessment requires information, and in many cases information about risks of a new technology is simply unavailable or uncertain. In such cases, the regulatory decision depends upon the default policy assumptions about the inherent safety of the technology. In turn, the default policy assumption is shaped by the framing of the new technology in relation to existing technologies.[9]

For example, in the 1980s, the FDA was faced with the decision of whether to regulate foods derived from genetically engineered crops. If genetic engineering was framed as a significant departure from conventional breeding techniques, the FDA could have chosen to regulate the new proteins introduced into genetically engineered foods as "food additives" under the Federal Food, Drug, and Cosmetic Act (FDCA), thereby triggering a mandatory pre-market approval of the food additive's safety. On the other hand, if genetic engineering was framed as being substantially the same as conventional breeding technologies, then the FDA could treat genetically engineered foods without a mandatory pre-market approval—the same as any other new variety of potato or whole food. With the latter approach, the relevant risk assessment question would not be whether the genetically engineered variety was safe; the question instead would be whether it was "as safe as" its conventionally produced counterpart. The level of information needed to support a finding of safety would have been significantly more demanding than the information required to make the assessment that a food was simply "as safe as" another variety.[10] Thus, FDA's risk assessment for genetically engineered foods depended to a significant extent on the policy decision to treat such foods as being comparable to new conventionally produced varieties.

B. Synthetic Biology: Framing and Risk Characterization

The initial framing question is whether the hazards posed by synthetic biology are similar to or qualitatively different from those posed by rDNA engineering or other genetic engineering techniques. Scientists have long argued that genetic engineering poses no unique environmental or public health risks, and that therefore the relevant regulatory question is the risk of the final product, not of how it was produced. Similarly, synthetic biology researchers argue that synthetic biology—particularly in its current state of development—is just an extension of rDNA and other genetic engineering techniques. Synthetic biology facilitates the manipulation of the structure of genetic elements and provides researchers with a more efficient means to engineer organisms. Engineered genetic pathways will still be based on naturally occurring components, and the engineered construct must still function within the confines of the biological requirements of a living organism. In the end, the final products—i.e., engineered organisms—are similar to those produced by other genetic engineering techniques. As a result, some synthetic biology researchers argue that there should be no distinction drawn between synthetic biology and other genetic engineering techniques.

As Benner states, "Much of what is currently called synthetic biology is congruent with recombinant DNA technology discussed in Asilomar 30 years ago. This includes bacteria that express heterologous genes, proteins in which amino acids have been replaced, and cells with altered regulatory pathways. Placing a new name on an old technology does not create a new hazard" (Benner & Sismour, 2005).

The emphasis on the continuity with past technology is a familiar pattern in the framing of a new technology. Similar arguments were made both with rDNA technology and nanotechnology.[11] The "not new" framing then becomes an argument for maintaining that existing regulations are sufficient to deal with the new technology.

Future developments in synthetic biology, however, could alter that view. Synthetic biology is likely to be not only a more efficient genetic engineering technology but also a means to engineer much more complex genetic modifications than can be accomplished through standard genetic engineering techniques. In addition, synthetic biology may enable the modifications of organisms with genetic elements designed from scratch that could have properties that are quite different from those that can be created through today's genetic engineering techniques. How far "natural" biologic limits can be stretched remains to be seen and is indeed a major focus of synthetic biology research. It is, of course, the very difference between synthetic biology and other genetic engineering techniques that makes its anticipated novel applications possible.

While synthetic biology provides more powerful tools for genetic engineering, there is no basis to assume that the novelty of the process itself poses new or enhanced risks. Instead, the kinds of genetically engineered products that are likely to be produced using synthetic biology are similar to those produced through other direct genetic engineering and conventional breeding techniques. The more relevant regulatory question, then, is whether the novel engineered organisms created through synthetic biology are likely to present new or enhanced risks compared to those of other genetic engineering techniques.

Most scientists believe that the biosafety risks of synthetic biology products are the same kinds of risks presented by products of other genetic engineering. For example, Serrano states that the risks associated with the accidental release of synthetic biology products are "in fact similar to the current biosafety problems associated with genetically modified crops, the use of engineered microorganisms to enhance production of desired targets etc." (Serrano, 2007).

"Other scientists are less confident about the ability to predict the survival and spread of synthetic microorganisms, particularly more complex organisms likely to be developed in the longer term."

What are the risks of genetically engineered organisms? Are organisms created through synthetic biology likely to pose different risks or a different level of risk? What are the risks associated with the likely first generation of synthetic biology products, such as synthetic microorganisms used to produce biofuels, industrial chemicals and pharmaceuticals?

1. Accidental Release Risk Assessment

The first risk scenario involves the accidental release of a synthetic microorganism[12] from a laboratory or other contained environment, such as a commercial bioreactor. Because such organisms are potentially capable of reproduction, evolution and spread through the environment, the risks of synthetic microorganisms, like other genetically engineered microorganisms in general, are different from those of conventional chemicals. If a synthetic microorganism is infectious, pathogenic, toxic or capable of reproduction, an accidental release could pose a risk to laboratory workers, the health of the adjacent communities, and the environment (Tucker & Zilinskas, 2006).

This issue is especially important for synthetic biology since the applications likely to emerge in the near future are microorganisms that are intended for contained use, either in academic or industrial research laboratories, or as part of a closed-end industrial production process to produce a final, often conventional, industrial or pharmaceutical chemical. Since these microorganisms will not be intended for use outside of a contained production facility, it will be important to assess the risks associated with an accidental release from such contained facilities.

An initial consideration in assessing the risk is the probability of a synthetic microorganism being able to reproduce and spread should it escape the contained environment. Some biological scientists assume that accidentally released synthetic microorganisms will pose a minimal risk because they are unlikely to survive in the natural environment.

> The more different an artificial living system is from natural biological systems, the less likely it is that the artificial system will survive in the natural world … The 30 years of experience with genetically altered organisms since Asilomar have indicated that virtually any human-engineered organism is less fit than its natural counterpart in the natural environment. If they survive at all in the environment, they do so either under the nurturing of an attentive human, or by ejecting their engineered features (Benner & Sismour, 2005).

Other scientists are less confident about the ability to predict the survival and spread of synthetic microorganisms, particularly more complex organisms likely to be developed in the longer term. Near-term products, derived from well-understood bacterial hosts and natural genetic sequences,

are likely to be comparable in risk to currently produced genetically engineered organisms. However, future synthetic organisms created from scratch "will lack a clear genetic pedigree and could have 'emergent properties' arising from the complex interactions of its constituent genes. Accordingly, the risks attending the accidental release of such an organism from the laboratory would be extremely difficult to assess in advance, including its possible spread into new ecological niches and the evolution of novel and potentially harmful characteristics"(Tucker & Zilinskas, 2006).

The potential future ability to construct organisms containing artificial DNA with non-conventional base pairs also raises questions about the ability of such organisms to survive, reproduce and spread if accidentally released. Some scientists argue that such organisms would be highly unlikely to survive. "[If] a completely synthetic life form ... has eight nucleotides in its genetic alphabet, [it] would find survival very difficult if it were to escape from the laboratory. What would it eat? Where would it get its unnatural nucleosides?" (Benner & Sismour, 2005).

A second element of a risk assessment is determining the hazard should an organism be accidentally released, become established, reproduce and spread. Not all engineered microorganisms would pose a health or an environmental risk if there was an accidental release. With rDNA molecular research, as with microbiological research in general, risk is assessed largely on the underlying risk of the donor or host organisms: for example, known pathogens obviously pose greater risk if released than benign organisms.[13] As a consequence, the NIH Guidelines for Research Involving Recombinant DNA Molecules (discussed in more detail below) require containment measures to be proportionate to the risk characteristics of the host or donor organisms. Organisms known to be extremely dangerous must be handled in the highest-level biosafety confinement laboratories. Thus the probability of a harmful accidental release is reduced by biosafety management practices intended to ensure containment and prevent the spread of dangerous infectious agents. While there have been rare reported incidents of harmful accidental releases of dangerous microbiological agents from laboratories,[14] the long and generally safe record of research laboratories in handling known dangerous agents should provide assurance that researchers have the capability to protect workers and the surrounding community from dangerous microorganisms, engineered or naturally occurring.[15]

2. Intentional Non-contained Use

The second risk scenario involves the potential health and environmental risks associated with a synthetic organism that has been designed for use in a non-contained setting. Examples include the use of synthetic microorganisms in fermentation ponds used for industrial chemical production, or applications such as microbial pesticides, bioprocessing agents to help sequester or capture carbon or bioremediation agents that would require use in the open environment. Unlike microorganisms intended solely for contained use, synthetic organisms intended for non-contained use will be specifically engineered to survive and function in the environment into which they are being released. As a result, they are more likely to be fit for survival and competition in the natural environment than organisms intended solely for contained use, making the risk of reproduction, spread and evolution more probable.

The potential environmental concerns about such synthetic microorganisms fall into several categories. One concern is that a synthetic microorganism designed for a particular task could interact with naturally occurring organisms and adversely affect the environment. This could occur if the synthetic organism infects or displaces existing organisms (including plants and animals), or otherwise interferes with the existing balance of the ecosystem into which it was released. If the synthetic organism establishes itself in an ecological niche, it might become difficult to eradicate. There is also a potential risk that some of the synthetic genetic traits could be spread through gene flow to other

natural microorganisms, resulting in the spread of unwanted traits or the inclusion of artificial genetic sequences in related organisms, if the trait provides a fitness advantage (Bhutkar, 2005; Tucker & Zilinskas, 2006).

In addition, the propensity of microorganisms to evolve when placed in an environment with multiple selective pressures creates problems. For synthetic biology engineers, the challenge is to find ways to prevent the microorganisms from evolving and potentially losing their engineered trait: after all, engineers want their inventions to remain stable and to continue to function as designed over many generations. For risk assessors, the potential for microorganisms to evolve creates additional uncertainties, since the pathway of evolution is difficult to predict. It is one thing to assess the environmental risk of the organism as designed, but quite another to try to predict what the organism could become many generations hence. Thus, developing ways to prevent the unwanted evolution of synthetic microorganisms is a challenge both for engineers and for risk regulators.

As with safety practices for rDNA molecules in laboratories, regulators have significant experience with assessing the risks of genetically engineered organisms intended for release into the environment. Over the last 25 years, USDA and EPA have reviewed and approved thousands of applications for field trials for experimental genetically modified plants and microorganisms. The type of review depends on the specific product and its intended use, but typically agencies assess such potential risks as toxicity, potential invasiveness, impacts on other organisms (insects, plants and animals) and the potential for unwanted gene flow to wild relatives. The risk assessment is based on a familiarity with the characteristics of host and donor organisms and vectors, consideration of the specific environment into which the organism is intended to be used and other factors. On the basis of the risk assessment, agencies typically impose restrictions on field trials of genetically engineered organisms to prevent their unintended spread and to minimize potential impacts on the environment.

However, regulators have had relatively little experience considering the potential risks posed by the eventual evolution of genetically engineered microorganisms intended for non-contained use. Anticipated environmental applications of genetically engineered microorganisms have not materialized in large part because of the technical difficulties of establishing functional microbial populations. The great majority of genetically modified organisms reviewed by the U.S. regulatory agencies in the past 25 years have been annual food crops. Biotechnology companies have specifically bred and tested these varieties to ensure the stable and predictable expression of the genetically modified traits. In addition, these crops are intended to be grown for a single season. As a result, evolution as a potential risk factor has not been relevant. Evolution is a much more relevant factor for genetically engineered microorganisms, but only a few such products have been approved by EPA for environmental use in the last 25 years.

The record of environmental risk regulation for genetically engineered organisms over the last 25 years is mixed. To be sure, there is no evidence to suggest that approved genetically engineered plants or microorganisms have created any public health or environmental problem (National Research Council, 2002). However, there have been several well-publicized cases that had the potential to adversely affect public health or the environment.[16] In addition, the regulatory system has failed to prevent low-level gene flow of both approved and experimental genetically engineered varieties of crops into conventional and organic food supplies.[17] While these instances have not created any apparent public health or environmental issue, they have resulted in significant economic losses to farmers whose crops have contained the unwanted genetic modifications. These issues demonstrate the difficulty of ensuring a zero gene-flow tolerance standard in agriculture.[18]

C. Comparing Risks of Biotechnology and Synthetic Biology

From the above analysis, it appears that the *nature* of the risks posed by synthetic biology products and other genetically engineered products is similar. For engineered microorganisms intended for contained use in a laboratory or an industrial setting, the major concern is that harmful organisms might be accidentally released and then reproduce and spread in the environment. For engineered microorganisms intended for non-contained use, the primary concern is the potential for environmental impacts on other microbes, plants and animals, and for unintended gene flow to natural organisms.

In both cases, the set of available risk management tools is the same. For engineered microorganisms intended for contained use in laboratories, the principal tool is containment—both physical and biological. The level of containment is determined by an assessment of the risk posed by the microorganism. For engineered organisms intended for use in the environment, regulators rely upon an assessment of potential environmental impacts to determine appropriate constraints on field trials or on general use intended to prevent unwanted gene flow and to minimize adverse environmental impacts.

In both instances, individualized risk assessment is the key to tailoring appropriate containment or other control measures to prevent unwanted consequences. But here is where there is a potential point of departure. Much of the risk analysis done by regulatory agencies for genetically engineered organisms is founded on the principle that its risk can be determined by comparison to its conventionally bred counterpart or naturally occurring genetic components. Since genetic engineering to date has largely involved the insertion or deletion of a relatively small number of genes, the host organism remains largely intact. A corn plant is still a corn plant, even if has been modified with *Bt* genetic sequences to express pesticidal proteins. Agencies also look at the known characteristics of the inserted or modified gene sequence to assess impacts on the organism, public health and the environment. The ability of agencies to assess potential public health and environment risks is based largely on knowledge about the underlying host and donor organisms, the transformation process and the functions of the modified genetic components.

Risk assessment becomes more challenging as an engineered organism becomes more complex, as novel gene sequences are introduced that have been significantly modified from known counterparts and as genetic components are assembled from a variety of sources, including those designed and built from scratch in a laboratory. Information about the behavior and characteristics of such organisms is likely to be more uncertain since there may be limitations on comparisons to previously known (and well-characterized) organisms or sequences. In addition, components of genetically engineered organisms assembled from various sources could interact in ways not predicted from the functions and behavior of those parts observed in their native sources. Considering the daunting complexity of living systems, "we can never rule out the possibility that new emergent and unexpected properties pop up when putting together parts that have been characterized in isolation or in a different context" (Serrano, 2007).

It is the ability of synthetic biology to create such complex organisms that raises issues about the ability of regulators to confidently assess the risk of some synthetic biology products. Some observers have predicted that "[b]ecause of a lack of empirical evidence, the inventor of a synthetic microorganism could not predict the effects of its release on human health and the environment with any degree of confidence" (Tucker & Zilinskas, 2006). These observers note that even if the source of all of the parts of a synthetic microorganism are known, and every new genetic circuit understood, it would be difficult to predict in advance whether the organism would have any unexpected emergent properties. As another report notes, synthetic biology may enable

"Little if any research has been done to predict the probability or impact of emergent properties of complex synthetic organisms."

the construction of a chimeric organism assembled from genetic material taken from hundreds of initial sources. "How to evaluate such constructions for biological safety remains murky" (Garfinkel, Endy, Epstein, & Friedman, 2007). It may be highly unlikely, for example, that a synthetic microorganism derived entirely from a variety of nonpathogenic sources could develop pathogenicity as an "emergent property," but the possibility cannot be entirely dismissed.[19] Little if any research has been done to predict the probability or impact of emergent properties of complex synthetic organisms.

Given this uncertainty, some researchers have called for a precautionary approach that treats synthetic microorganisms as dangerous until proven harmless (Tucker & Zilinskas, 2006). In 2005, one prominent researcher in the area, George Church, argued that researchers should "imagine worst-case scenarios," cripple microorganisms to prevent them from being able to reproduce if accidentally released and institute "full physical isolation and confined lab experiments on human or agricultural pathogens" until more data is obtained on potential ecological and biomedical consequences (Church, 2005).

The issue is not whether synthetic microorganisms can be safely contained in the laboratory; long experience with highly virulent pathogens shows that they can. But imposing the highest level of biosafety containment requirements, in the absence of the ability to classify the risk of a microorganism, would clearly impose significant costs that are likely to be unnecessary. A maximum precautionary approach would provide the highest level of safety, but at the cost of severely, and almost certainly unnecessarily, impeding research and the development of potentially beneficial products. On the other hand, minimal biosecurity requirements would permit the most research to proceed, but risk the possibility of a harmful accidental release.

For complex synthetic microorganisms intended for use in non-contained environments, risk assessment poses equally difficult challenges for regulators and risk managers. Environmental risk assessment relies upon information about the known environmental characteristics and behaviors of introduced organisms, their expressed traits and the nature of the ecosystem into which the organism is intended to be introduced. At some point, the more that a genetically engineered organism departs from a known host or donor organism or genetic sequence, the more difficult it will be for risk assessors to predict the environmental characteristics of the engineered organism based on such knowledge. Since containment measures in the field are not as effective as those in the lab (National Research Council, 2005), how can regulators assess and manage risk in the absence of information about the product's risk characteristics?

Thus, while the risks of genetically engineered organisms produced through synthetic biology and other genetic engineering techniques appear to be of the same kind and nature, requiring similar risk assessment and risk management approaches, the complexity made possible by synthetic biology creates uncertainty for conducting risk assessments needed to design appropriate containment or controls. Faced with uncertainty, risk managers will almost certainly either over-regulate, by imposing unnecessary and costly burdens that will slow research without providing any additional protection, or under-regulate, by letting risky research or testing proceed without appropriate safeguards.

IV. Applying the Biotechnology Regulatory Framework to Synthetic Biology

A. Developing the Policy Framework for the Regulation of Biotechnology

There appears to be a widespread assumption in the synthetic biology community that the regulatory model for rDNA biotechnology is an appropriate one for synthetic biology, and that in fact it already applies to synthetic biology products (Garfinkel, Endy, Epstein, & Friedman, 2007). This section will examine the applicability of the current biotechnology regulatory structure to the synthetic microorganisms that are likely to be the first products of synthetic biology and the issues raised by managing the potential risks of synthetic biology products through this approach.

The history of the development of the policy and regulatory framework for biotechnology has great relevance to synthetic biology. The development of biotechnology regulation from initial efforts at self-regulation, to external scientific oversight and, ultimately, to federal regulation, has parallels to synthetic biology.

The molecular biologists gathered at Asilomar in 1975 called for restraint and self-regulation in certain areas of rDNA research. Like all efforts at self-regulation, the Asilomar proposal reflected mixed motives. To be sure, the scientists were sincerely concerned about protecting the health of lab workers, the public and the environment, and believed that their expertise put them in the best position to assess and manage the risks associated with their research. But the scientists were also excited about the opportunities in this new area of research and wanted to be able to pursue it without government oversight or regulation that could slow it down. They also understood that public concerns about the safety of biotechnology research could hinder their research and believed that their proactive approach to the issues would reassure the public that the scientific community was being responsible and taking those concerns seriously. The call for self-regulation was motivated both by genuine concern about safety and by self-interest in protecting their research from outside interference (Wright, 2001; Berg, 2001). After some time, however, it became apparent that self-regulation by itself would not be enough to create public confidence in the safety of biotechnology. The public is often skeptical about the adequacy of self-regulatory efforts, in part because of the perception of a conflict of interest among those regulating themselves. Self-regulatory efforts often lack credibility because there are no enforcement mechanisms or sufficient penalties for noncompliance. Recent public opinion polls on nanotechnology confirm that the majority of the public believes that self-regulation is insufficient to ensure the safety of emerging regulation (Macoubrie, 2006). Finally, even well-motivated and competent scientists may not be the best judges of the potential risks of their own research, either because self-interest biases their judgments or because they fail to recognize risk factors outside of their area of expertise. Studies have shown that technology developers have little contact with people assessing risks downstream and tend to overestimate the level of control they have (Powell, 2007).

Leaders in the molecular biology community called for the National Institutes of Health to establish a Recombinant Advisory Committee

(RAC) to provide independent federal scientific oversight of proposed rDNA research and to establish standardized safety guidelines for researchers. The NIH published the initial Guidelines in 1975.[20] RAC was conceived as solely a scientific review process; however, congressional and public concerns led to the appointment of additional, nonscientist representatives to the RAC. Initially, the Guidelines were quite conservative, but as experience grew with genetic technologies, confidence was gained that many experiments could be conducted with minimal risk, and the Guidelines were relaxed (Talbot, 1981). Over time, the RAC delegated much of its review authority for "routine" rDNA experimental proposals to local institutional biosafety committees (see Box 1). Today, most rDNA research at NIH-funded institutions is reviewed solely by their respective IBCs.

The NIH Guidelines remain the authoritative source of safety guidance for laboratory research funded by the NIH and other government agencies. The application of the NIH Guidelines to synthetic biology research is discussed in more detail below.

BOX 1

Institutional Biosafety Committees

Under the NIH rules, each research institution receiving funding from the NIH is required to institute biosafety procedures and to establish an institutional biosafety committee (IBC). The role of the IBC is to ensure "local" institutional compliance with the NIH Guidelines. The IBC reviews rDNA research being conducted at the institution, approves certain research proposals and ensures that they are consistent with the NIH Guidelines. Under NIH rules, the IBC must consist of no fewer than five individuals, including at least two members not affiliated with the institution, and collectively represent appropriate rDNA expertise. As appropriate depending on the nature and scale of the research conducted at the institution, IBC members may be required to include the institution's biosafety officer, plant and animal experts and experts in assessment of environmental and public health risks. If required by the nature of the research, the IBC may also consult with ad hoc experts.

Depending on the organism being used and the level of risk of the proposed research involving rDNA molecules, as determined by application of the NIH Guidelines, the principal investigator may be required to notify the IBC or to obtain IBC approval before initiating the research. (Some research is exempt, a determination that may be left to the principal investigator.) In certain cases involving novel issues or higher risk, prior review or approval may also be required by the NIH or the NIH RAC. In reviewing or approving proposed rDNA research, the IBCs determine the appropriate biological and physical containment levels, applying the NIH Guidelines, and ensure adequate biosafety safeguards, including training and reporting.

Institutions are required to register the IBC with NIH's Office of Biotechnology Activities, to provide a roster of IBS members and their backgrounds and to update the NIH on an annual basis. The IBCs are required to meet regularly, to keep minutes (which must be publically available on request), and "when possible and consistent with protection of privacy and proprietary interests," to open IBC meetings to the public. The research institution is required to report any significant problems or violations to the NIH's Office of Biotechnology Activities within 30 days.

The NIH Guidelines served to manage the risks of contained laboratory research using rDNA technology throughout the 1970s and early 1980s. In the early 1980s, however, when the first genetically modified organisms were emerging from the laboratory into field testing in the open environment, it became clear that, as a science funding agency, the NIH was not an appropriate agency for regulating intentional releases of genetically modified organisms into the environment, particularly commercial products.[21] To fill the void, the White House Office of Science and Technology Policy (OSTP) shepherded the development of the "Coordinated Framework" for the regulation of biotechnology products in the United States. In addition, the Coordinated Framework was supported by biotechnology companies that understood that some external governmental review would help build public trust for commercial biotechnology products. The Reagan administration and

the biotechnology industry rejected the notion, promoted by some in Congress and in public interest groups, that existing laws were inadequate and that new legislation was needed. Opposed by the administration, proposals to pass new laws did not go far in Congress.[22]

The agencies faced a daunting challenge in interpreting their existing legal authorities to implement the Coordinated Framework policies. While the policy decision to regulate products rather than process had been made, the regulatory agencies still faced the question of how biotechnology products should be categorized for the purposes of regulatory review. The power of biotechnology in part was the ability to create products that had never been seen before—such as a corn plant that produces its own insecticide, a cow that manufactures a human vaccine or a fish engineered to grow three times faster than wild varieties. As noted previously, FDA decided to treat genetically modified foods as functionally equivalent whole foods, rather than as food additives. EPA faced similar choices. To regulate genetically modified microorganisms, EPA decided that novel arrangements of DNA would be considered a "new chemical substance" under the Toxic Substances Control Act (TSCA)—an interpretation with the potential to bring all novel life forms under EPA's authority to regulate toxic chemicals. Similarly, while the EPA has no authority over plants, it decided to regulate the pesticidal protein expressed within each cell of the genetically modified corn crop as a pesticide subject to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). USDA, for its part, regulated genetically modified plants under its authority to control potential plant pests. On the animal side, the FDA decided to regulate genetically modified animals under its authority to regulate new animal drugs under the Food, Drug and Cosmetics Act (FDCA), on the theory that the gene inserted into the animal and its expressed protein was an animal drug, despite the fact that it is also an inheritable trait. All of these categorization decisions had significant implications for the regulatory pathway a biotechnology product would follow.

B. Applying Biotechnology Policy and Regulation to Synthetic Biology

How well do the policies, laws and regulations developed for biotechnology products fit the likely first generation microbial products of synthetic biology? Are such products covered? Do the agencies have adequate authority to assess and manage the risks of synthetic microorganisms? If they have adequate authority, do they have sufficient technical and budget resources to exercise it?

For the purposes of this analysis, we have divided the application of existing federal laws and regulations to synthetic biology into three categories that are intended to cover the range of potential risks: (1) accidental release in a contained research setting; (2) accidental release from a contained industrial production facility; and (3) intentional uses in a non-contained setting or a release into the environment. Within those categories, the application of laws to specific product types will be considered (Table 4).[23]

1. Research and Development Activities in Contained Facilities

One of the risk scenarios for synthetic biology is the accidental release of a harmful synthetic microorganism into the environment from a research laboratory. Similar concerns about genetically engineered microorganisms led to the development of a number of policies and regulations designed, in part, to prevent that risk. To what extent do these policies and regulations also apply to R&D activities with synthetic biology in contained facilities?

a. Generally Applicable Laws and Regulations

A number of laws and regulations, while not adopted specifically to address genetically engineered organisms, have relevance to research

laboratory biosafety, including synthetic biology research. For example, new biosecurity laws and regulations adopted over the last several years impose restrictions and require reporting for possession of specified "select agents" that could be used in bioterrorism.[24] Laboratories working with those agents, or synthesizing DNA segments of such agents, would be covered by such rules. In addition, the Occupational Safety and Health Administration has issued rules intended to protect employees from transmission of certain infectious blood-borne diseases such as HIV and hepatitis (see 29 C.F.R. Part 1910.1030). Of course, private research laboratories are required to comply with other general federal and state environmental, public health and labor laws and regulations. In addition, under common tort law, companies would be liable to compensate for any damages caused by negligent activities, including the negligent handling of potentially hazardous synthetic microorganisms. In such a case, the NIH Guidelines, among other sources, are likely to define the "reasonable standard of care" to which researchers should adhere.

b. NIH Guidelines for Research Using rDNA Molecules

The NIH Guidelines were developed as the primary line of defense against the potential accidental release of experimental genetically engineered organisms. To what extent do these guidelines apply to research on synthetic biology?

TABLE 4. REGULATION OF SYNTHETIC BIOLOGY PRODUCTS UNDER U.S. BIOTECHNOLOGY FRAMEWORK

Product	Scope	Agency / Authority	Legal Tools	Comments	Risk Management Issues
R&D in Contained Facility					
NIH or federally-funded research	all R&D with rDNA molecules (*proposed: synthetic nucleic acids)*	NIH Guidelines & IBCs	Contract; violations threaten future federal funding	Reliance on IBCs and self-reporting	Uncertainty of risk; guidance to IBCs
Privately-funded basic				Not covered directly	
Industrial chemicals - commercial R&D	covered intergeneric microorganisms not regulated by other agencies (i.e., drugs)	EPA TSCA	Pre-manufacturing notification	Exempt if comply with NIH or functional equivalent; definition may not cover synthetic microorganisms	Relies on NIH; uncertainty in risk assessment; agency must show risk; limited resources
Human or animal drugs, biologics, medical devices	all (functional definition)	FDA FDCA	Mandatory pre-market approval; approval for investigational new drugs and devices	Some pre-commercial research phase not covered	
Commercial Production or Use in Contained Facility					
Human or animal drugs, biologics, medical devices	all (functional definition)	FDA FDCA	Can withdraw product approval; regs for good manufacturing practices; reporting		Limited resources
Industrial chemicals - commercial R&D	covered intergeneric microorganisms not regulated by other agencies (i.e., drugs)	EPA TSCA	Pre-manufacturing notification	Certain low-risk microorganisms in containment are exempt	Uncertainty in risk assessment; agency must show risk; resources
Microbial pesticides	all (functional definition); modified microbes	EPA FIFRA	Prior approval for use in non-contained facility	Exempts testing in facilities meeting NIH Guidelines or functional equivalent	Authority to require developer to test for environmental risks
Use in Non-Contained Settings					
Non-commercial research	GE microorganisms of unknown or unclassified organism	USDA APHIS	Permit required for transport or field trials	Does not cover public health risk	Uncertainty re: environmental risk assessment
Human or animal drugs, biologics, medical devices	all (functional definition)	FDA FDCA; NEPA	Mandatory pre-market approval for safety	Limited environmental authority	Clinical trials for safety and efficacy; environmental risk info limited
Industrial chemicals - commercial R&D	covered intergeneric microorganisms not regulated by other agencies (i.e., drugs)	EPA TSCA; USDA APHIS; NEPA	Pre-manufacturing notification; pre-release approval	Exempts some low-risk field trials; excludes noncommercial releases; overlap with APHIS	Uncertainty in risk assessment; agency must show risk; limited resources
Microbial pesticides	all (functional definition); modified microbes	EPA FIFRA	Mandatory pre-market approval for unreasonable risk; prior approval for field trials		Authority to require developer to test for environmental risks
Microbial animal and plant pests	GE microorganisms of unknown or unclassified organism	USDA APHIS; NEPA	Notification or permit for field trials; deregulation for commercialization	Does not cover public health risk	EIS might be required

TABLE 5. NIH CLASSIFICATION OF BIOHAZARDOUS AGENTS BY RISK GROUPS

Risk Group 1	Risk Group 2	Risk Group 3	Risk Group 4
Agents that are not associated with disease in healthy adult humans	Agents that are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are *often* available	Agents that are associated with serious or lethal human disease for which preventive or therapeutic interventions *may be* available (high individual risk but low community risk)	Agents that are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are *not usually* available (high individual risk and high community risk)

Source: NIH Guidelines for Research Involving Recombinant DNA Molecules, Appendix B, Classification of Human Etiologic Agents on the Basis of Hazard.

This same question was recently posed by the National Science Advisory Board for Biosecurity (NSABB).[25] Following a workshop in October 2007, the NIH RAC Biosafety Working Group developed draft recommendations for revising the NIH Guidelines to ensure their applicability to synthetic biology research and to provide guidance for biosafety practices, which were adopted by the RAC in March, 2008 (Rosenberg & Corrigan-Curay, 2008).[26]

The purpose of the proposed revisions, according to the NIH RAC Biosafety Working Group's recommendations, is to ensure that the NIH Guidelines "capture the same products made by synthetic techniques that are currently covered under the scope of rDNA research, provided that the same biosafety concerns are raised," and to develop a risk management framework for synthetic biology research.

The RAC Biosafety Working Group proposal includes a revision of the current definition of "rDNA molecule" to capture synthetic biology research that might not otherwise be included. The current NIH Guidelines define "recombinant DNA molecules" as "(1) molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (2) molecules that result from the replication of those described in (1) above" (Section 1-B).

The RAC Biosafety Working Group saw several deficiencies in the current Guidelines as they apply to synthetic biology research. For example, the proposed revisions would include all synthetic nucleic acids, and add synthetic nucleic acids that can be created without joining segments, such as those that contain functional analogs of nucleotides. The proposed revised definition would cover both recombinant and synthetic nucleic acids, defined as "(i) Recombinant nucleic acid molecules are molecules that are constructed by joining nucleic acid molecules and can replicate in a living cell, (ii) Synthetic nucleic acids are nucleic acids that are chemically synthesized or amplified and may solely or partially contain functional equivalents of nucleotides, and (iii) molecules that result from the replication of those described in (i) or (ii) above." This broader definition would appear to cover synthetic genetic constructions that could pose a risk if not properly managed.

While synthetic microorganisms would be covered by these revisions to the NIH Guidelines, there are other questions relating to the Guidelines' scope and application, some of which were addressed by the NIH RAC Biosafety Working Group. At the heart of the Guidelines is the process for characterizing the risk of the organism (or "agent," the term used in the Guidelines) that is the subject of the research, which in turn determines the appropriate levels of biosafety procedures and containment. The most significant element of the risk characterization is the safety of the agent being modified (Table 5).

Increasing levels of containment are required as an agent becomes more seriously pathogenic to humans. The Guidelines note that the factors to be considered in determining the level of containment include agent factors such as "virulence, pathogenicity, infectious dose, environmental stability, route of spread, communicability, operations, quantity, and

availability of vaccine or treatment, and gene product effects such as toxicity, physiological activity, and allergenicity" (Section II-A-3). There are additional considerations for research on microorganisms, viruses, plants and animals that might pose a risk to plant and animal health if accidentally released.

The difficulty of applying this process to synthetic microorganisms is that it assumes knowledge about the risks (such as virulence) of the particular organism being modified. As noted previously, it may be difficult to characterize the risk of a chimeric organism that has been assembled from scratch or from multiple sources. The more that a synthetic organism or its components differ from known sequences, the more difficult it may be to confidently predict its behavior. In view of this concern, the NIH RAC Biosafety Working Group proposed the following changes to the NIH Guideline provisions addressing risk assessment:

> While the initial RA [risk assessment] is based on the identification of the RG [risk group] of the parent agent, as technology moves forward, it may be possible to develop a chimera in which the parent agent may not be obvious. In such cases, the risk assessment should involve at least two levels of analysis. The first involving a consideration of the RGs [risk groups] of the source(s) of the sequences and the second an analysis of the functional attributes of these sequences (e.g., sequence associated with virulence factors, transmissibility, etc.). It may be prudent to first consider the highest risk group classification of any agent sequence included in the chimera. Other factors to be considered include the percentage of the genome contributed by each of the multiple parent agents and the predicted function or intended purpose of each contributing sequence. The initial assumption should be that such a sequence will function as predicted in the original host context. The IBC must also be cognizant that the introduction of the combination of certain sequences may result in a new organism whose risk profile could be higher than that of the contributing organisms or sequences. The synergistic function of the sequences may be one of the key attributes to consider in deciding whether a higher containment level is warranted. A new risk may occur with a chimera formed through combination of sequences of a number of organisms or combining of transgenes that direct the acquisition of the new phenotype (Rosenberg & Corrigan-Curay, 2008).

While the Biosafety Working Group proposal provides additional needed guidance, it is striking to see how it relies upon assumptions and precautionary principles in implicit recognition of risk uncertainties. The proposal states that it would be "prudent" to first consider the highest-risk group of any source of genetic material. It also states that the "initial assumption" should be that such sequences will have the same function as they had in the original host, while at the same time recognizing that there could be a synergistic function that leads to a higher risk profile than that of contributing organisms or sequences. In essence, the Guidelines recommend that the IBCs take a pragmatic but precautionary approach in response to uncertainty about synthetic organisms.

The application of the NIH Guidelines to synthetic biology research also raises questions about the role of the IBCs, which have expanded over the years to take on new emerging concerns about research, including biosecurity and bioterrorism. Adding review of synthetic biology research to the IBCs' responsibility, while entirely appropriate, will create additional demands on an already-strained IBC system. To be able to understand and appropriately assess the risk of synthetic biology, even with the benefit of NIH's broad guidance, the IBC would need to contain experts with the broad array of expertise from multiple scientific and engineering disciplines often involved with synthetic biology research. It is unclear whether the existing IBCs have the expertise needed to independently evaluate the risks presented by a particular synthetic biology research proposal.

Finally, the inherent limits of the NIH Guideline process should be noted. Researchers who choose to do so can bypass NIH and IBC review by obtaining non-federal funding. Compliance with the NIH Guidelines is enforceable only as a contractual provision in a grant agreement; the

sanctions for violations include a suspension of funding for additional rDNA research at the institution. The impact of this sanction will depend on the extent to which the institution relies upon NIH as the funder. The NIH is not a regulatory agency and lacks the resources to ensure that grantees are in full compliance with the NIH Guidelines, and instead relies upon self-reporting of problems or violations from funded institutions. While the biosafety record for biotechnology research under the NIH Guidelines has generally been quite good,[27] some may question whether the Guidelines provide sufficient incentives to ensure compliance.

c. New Chemicals under the Toxic Substances Control Act

Under the Coordinated Framework for biotechnology products developed by the Reagan administration in the mid-1980s, the Toxic Substances Control Act (TSCA) (15 U.S.C. §2601) was widely expected to be the "catch-all" law for genetically modified organisms not otherwise covered by other statutes.

Congress passed TSCA in 1976 in the wake of highly publicized disclosures about the toxicity and environmental impacts of widely used chemicals such as dioxins and asbestos. TSCA was intended to provide a way for EPA to screen for and then control the most toxic chemicals already in commerce and to prevent risks from new unregulated chemicals coming on the market.[28] Section 4 of TSCA gives EPA the authority to require companies to test existing chemicals, and section 6 gives EPA the authority to control "unreasonable risks" posed by existing chemicals. Of greatest relevance to biotechnology products is section 5, which gives EPA the power to screen and track non-exempt new chemical products before they come onto the market. Section 5 requires manufacturers, importers and processors to notify EPA at least 90 days in advance of producing or importing a "new" chemical substance, defined as one not included in EPA's inventory of existing chemical substances.[29] Along with the notification, manufacturers are required to provide EPA with any information or test data on chemicals that "are known to, reasonably ascertainable by, or in possession of the notifier" that might be relevant to EPA's risk assessment. At that point, EPA has 45 days to assess the new chemical's potential risk and determine whether the new chemical substance "presents or will present an unreasonable risk" and impose restrictions. EPA may require similar notifications and may impose similar restrictions upon existing chemicals (that is, chemicals already listed on EPA's inventory) if that chemical has a "significant new use."

In 1997, EPA finalized rules, initially proposed in 1986, that applied section 5 to genetically engineered microorganisms, such as microbes used for bioremediation, oil recovery, biomass conversion and biosensing, or for specialty chemical and enzyme production.[30] In interpreting TSCA, EPA argued in its rules that DNA is a chemical substance, and that new, non-natural arrangements of DNA constitute a "new chemical substance" under TSCA.[31] Under the rules, the creation and replication of a genetically engineered microorganism was considered to be the functional equivalent of "production and manufacture" of a new conventional chemical, and thus would trigger the requirement to notify the agency and begin the agency's risk review process. EPA created a special notification process for genetically engineered microorganisms called the Microbial Commercial Activity Notice (MCAN). A MCAN must be submitted to EPA at least 90 days before the genetically engineered microorganisms are produced for a commercial purpose. In addition, EPA's regulations require the agency to be notified through a TSCA Experimental Release Application (TERA) before any testing of a covered genetically engineered microorganism outside of a non-contained facility.

Do EPA's rules for microbial products of biotechnology under TSCA apply to synthetic biology microorganisms, and, if so, would they adequately address the potential risk of accidental releases from contained R&D activities?

A threshold question is whether EPA's rules would apply to synthetic microorganisms. EPA's rules apply to an "intergeneric microorganism," defined as "a microorganism that is formed by

the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera."[32] In developing this definition, EPA argued that new microorganisms created from combinations of genetic material from distantly related organisms would have a higher probability of exhibiting a new trait or a new combination of traits, and that the behavior of such combinations would be significantly less predictable than that of microorganisms created by combining genetic materials from closely related microorganisms, warranting regulatory review (62 Fed. Reg. 17910 (1997)).

While the same logic would apply to synthetic microorganisms, EPA's definition may not cover some of them. The definition presupposes that the genetic materials are derived from existing natural organisms in different taxonomic genera and then combined. What about the case where a DNA segment is entirely artificial and not taken from another existing organism? On its face, such a microorganism would not seem to be covered by EPA's definition.

An alternative interpretation could, however, cover such synthetic microorganisms. Under this interpretation, a genetically engineered microorganism would be excluded only if all of its material comes from within the same genus. Thus, the addition of any genetic material from outside the host's genus—regardless of its source—would be covered. This interpretation would be consistent with EPA's stated justification for the rule.

In either event, as applied by EPA, the TSCA definition of "new chemical substances" is broad enough to cover synthetic microorganisms; EPA might need only to modify its rules on genetically engineered microorganisms to clarify its coverage of the full range of synthetic microorganisms.

Assuming that EPA's rules cover synthetic microorganisms, how do they apply to synthetic biology R&D in contained facilities such as research laboratories? In developing its rule for genetically engineered microorganisms, EPA was clearly concerned about the potential for public health and environmental harm of an accidental release from the contained facility. However, EPA had to navigate two legal hurdles in order to cover genetically engineered microbes in research laboratory settings. First, TSCA requires section 5 pre-manufacturing notices only for the manufacturing and processing of new chemical substances for "*commercial* purposes" (15 U.S.C. §2607(f)). In addition, TSCA exempts small quantities of chemicals manufactured or processed solely for the purpose of "scientific experimentation or analysis" or "chemical research on, or analysis of such substance or another substance, including such research or analysis for the development of a product," provided that the manufacturer notify researchers of any known health risks (15 U.S.C. §2607(a)(1)(B)(ii)).

On their face, these provisions would appear to exempt much of the early research and development stages for both genetically engineered and synthetic microorganisms. In its rules on genetically engineered microorganisms, however, EPA interpreted these provisions in a way to ensure that many research activities could be covered if needed to address biosafety issues.

First, EPA's rule specifically covers "commercial research and development" activities, which EPA construes broadly to include all R&D activities that "are funded directly, in whole or in part, by a commercial entity regardless of who was actually conducting the research" (40 C.F.R. §725.205). In other words, EPA presumes a commercial purpose for any research activity funded in whole or in part by a commercial entity. Thus, a university research project that receives funds from both the public sector and a commercial entity would be covered by EPA's regulations. Even in the absence of commercial funding, EPA considers R&D activities to be commercial if they are "conducted with the purpose of obtaining an immediate or *eventual* commercial advantage for the researcher" (emphasis added).[33] Thus, only the most basic knowledge-seeking research funded solely by the public sector or a non-commercial entity would be exempted from EPA's notification rules on genetically modified organisms.

Similarly, in its rule, EPA recognizes that the "small quantity" exemption was problematic for genetically engineered organisms, given that even a small number of accidentally released microorganisms could become established and spread (62 Fed. Reg. 17909, 17923 [April 11,

1997]). Instead of focusing on quantity, the EPA rules focus on containment, exempting R&D within a contained structure.[34] EPA exempts contained R&D activities on genetically modified microorganisms that are required to comply with the NIH Guidelines (40 C.F.R. §725.232) or that have functionally comparable biosafety and containment procedures in place, provided that records were kept and researchers were notified of any known health risks (40 C.F.R. §725.234).

The net effect of EPA's rules is that research with genetically engineered microbes is exempted from TSCA notification requirements as long as the activities are in a contained facility that complies with the NIH Guidelines or their functional equivalent. Thus TSCA is intended to be used to cover research that is not already covered by the NIH Guidelines or their functional equivalent. Developers creating genetically engineered microorganisms in non-contained structures would be required to file a MCAN with EPA before they created or reproduced a covered genetically engineered microorganism. (The MCAN requirements are discussed in a later section.)

The EPA R&D exemptions raise several issues. First, they defer to the NIH Guidelines. The limitations of the NIH Guidelines were discussed in the previous section. In particular, even if the proposed revisions to the NIH Guidelines are adopted, thereby covering synthetic nucleic acids and organisms, the Guidelines leave a great deal of discretion to the IBCs in assessing and managing the risks of synthetic microorganisms. Second, EPA does not have the resources to monitor compliance by those institutions not covered by the NIH Guidelines. As a practical matter, EPA must rely upon those institutions to comply, with the threat of penalties should an accident occur.

Finally, EPA's jurisdiction is limited; it covers only part of the spectrum of potential synthetic microbial products. In particular, EPA can regulate only those microorganisms not under the jurisdiction of other agencies. Thus, synthetic biology research and development that may have potential biomedical applications would fall under the jurisdiction of the FDA. Microbes intended for use as pesticides would fall under the separate pesticide laws administered by the EPA. Therefore, the adequacy of oversight of R&D biosafety for those types of synthetic microbes must be separately considered.

d. Drugs and Other Products under the Federal Food, Drug, and Cosmetic Act

Under the Coordinated Framework policy approach, biotechnology products that are intended for use as food, food additives, animal feed, drugs, human biologics, cosmetics or medical devices are subject to regulation by the FDA under various provisions of the Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. §301 *et seq.*).

The FDCA provides the FDA with broad authority to regulate the safety and efficacy of human and animal drugs and medical devices. Before drugs or medical devices can be marketed, FDA must find them to be both safe and effective (FDCA §505(a); §512(a)(1)). The burden of proof is on the developer. As discussed in the next section, FDA also has significant authority to regulate the drug and drug device manufacturing process to ensure safety once a discovery moves into the commercialization stage.

While FDA's authority is broad, it is not unlimited. In the research-to-commercialization process, FDA's authority begins to apply at the point where a potential product begins to move down a commercialization pathway and testing is required to determine safety and efficacy. At that point, prior to testing, investigators are required to seek FDA approval for investigational use of a new drug or medical device (§505(i); §512(j); §520(g)). The FDA may require reports to ensure the safe use of the product during the investigational period and clinical trials. The FDA has indicated that drugs and biologics using rDNA technology "should generally follow" the NIH Guidelines, but FDA does not appear to have clear authority to require such compliance at an early research stage before safety and efficacy testing (HHS, Food and Drug Administration, 1985; Korwek, 1981).

For such early-stage research on potential products covered by the FDCA, the NIH

Guidelines would apply to federally funded research. While pre-commercial, basic biomedical private sector research on genetically engineered organisms is not required to comply with NIH Guidelines, industry has its own commercial, economic and legal incentives to comply with biosafety requirements.

e. Conclusions About Contained R&D

Applying the current system of biotechnology regulation to synthetic microorganisms leads to several conclusions. Most significantly, the NIH Guidelines are the critical line of defense against the risk of an accidental release of a synthetic microorganism from a contained research facility. The NIH Guidelines apply to all institutions receiving support for rDNA research from NIH or other federal agencies. While the Guidelines do not directly apply to research funded solely by the private sector, they constitute the standard of practice for biosafety risk assessment and management. EPA exempts developers from notifying the agency about covered synthetic microorganisms as long as the R&D activities are in a facility directly covered by the NIH Guidelines or one meeting its functional equivalent. FDA urges private sector researchers conducting early biomedical research with genetically engineered microorganisms to comply with the NIH Guidelines.

Given the fundamental importance of the NIH Guidelines to synthetic biology biosafety, it is all the more important for NIH to quickly complete its review of the Guidelines as they apply to synthetic biology. At the same time, the NIH Guidelines, even revised as proposed, are limited by the challenge of characterizing the potential risk of complex organisms engineered through synthetic biology. The heart of the Guidelines is the ability to assess the risk of proposed research and to define the appropriate level of containment. The ability of synthetic biology to create complex organisms with genetic contributions from multiple sources and possible synergistic properties makes risk assessment more uncertain. While synthetic organisms as a class are unlikely to pose novel risks or greater levels of risk than other genetically engineered organisms, the greater uncertainty of the risk assessment will require NIH to provide clearer policy guidance to IBCs on the level of precaution to take.

2. Commercial or industrial production using synthetic microorganisms in a contained facility

Scientists have been using genetic engineering for some time to create microbes that can function as production platforms, expressing chemicals with valuable biomedical or industrial qualities. In 1982, Genentech received FDA approval for insulin produced by a genetically engineered *Escherichia coli* bacterium. Developers hope to be able to use synthetic biology in the same way and to overcome some of the hurdles faced using recombinant DNA techniques.

The production of drugs and other chemicals from genetically engineered microorganisms is typically done in highly controlled, confined structures, including bioreactors and fermenters. The same kind of production techniques are expected to be used for synthetic organisms. However, most of the genetically engineered microorganisms used in industrial production pose a very low risk, and would be unlikely to survive if accidentally released. Given the low risk of the organisms, most production facilities are operated at lower biosafety levels than research laboratories that handle more dangerous or uncertain organisms. How would regulations developed for genetically engineered microorganisms in industrial production processes address the potential for an accidental release of a synthetic microorganism used in a similar way?

a. Drugs and Medical Devices under the FDCA

Under the FDCA, the FDA has broad authority to regulate the manufacture and production of human and animal drugs to ensure quality, safety and consistency (§501(a)(1)(B); §512(f)(1)(A)). The FDCA also declares a drug "adulterated" if "the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practices" (§501(a)(2)(b)).

FDA has issued numerous industry guidances and developed "good manufacturing practices"

that are intended to ensure the safety of the drugs as well as of the drug production process. The manufacturer is also required to get FDA approval for any change in the manufacturing process. Therefore, even if FDA has approved a particular drug, a new way of producing it—such as using a synthetic microorganism—would require separate FDA approval. FDA would have adequate authority to impose biosafety guidelines not only to ensure the quality of the drug but also to protect worker safety and the public health from the drug manufacturing process (HHS, Food and Drug Adminstration, 1985). For example, FDA could impose containment or other measures designed to prevent risks associated with accidental releases. Drugs and other products covered by the FDA have been safely produced from genetically engineered microorganisms for over 20 years.

While FDA has adequate authority to impose containment requirements and other methods to ensure overall safety, what those requirements are will depend on a risk assessment of the organism. Presumably, any microorganism designed for use in a production facility will be engineered to have relatively little risk of infection, pathogenicity or toxicity so that the organism can be safely used in production facilities at relatively low levels of biosafety precautions. Manufacturers are unlikely to be interested in using a synthetic microorganism that would require costly biosafety precautions. The critical question is whether there will be adequate information to assess in advance the potential risk of any synthetic microorganism, particularly complex synthetic microorganisms assembled from a large variety of genetic sources. It is unclear what, if any, restrictions or controls FDA would require for such products under its jurisdiction.

b. Industrial Chemicals under TSCA

Through regulations, EPA has applied TSCA to genetically engineered microorganisms used to produce industrial chemicals. Even if the final industrial product is a conventional chemical on EPA's existing chemical inventory, the genetically engineered microorganism used in the production process to make it would itself be considered a new chemical substance subject to TSCA. The creation and reproduction of the genetically engineered organism would itself be considered manufacturing or processing under TSCA.

However, many genetically engineered microbes currently used in industrial production facilities are exempted from TSCA's notification requirements because EPA has determined in its rule that they do not pose an "unreasonable risk." EPA's rules specifically exempt certain defined low-risk organisms, provided that they are used in a facility that meets specified physical containment and control facilities (40 C.F.R.§725.400 et seq.).[35] Manufacturers meeting these requirements may file a certification with EPA that exempts them from other reporting and notification requirements.

If the production process does not meet EPA's exemption criteria, however, the manufacturer would be required to notify the agency before manufacturing the genetically engineered microorganism. EPA has developed a special notice for genetically engineered microbes, entitled a Microbial Commercial Activities Notification (MCAN) (40 C.F.R. §725.100 et seq.). Under this regulation, a MCAN must be submitted to EPA at least 90 calendar days prior to manufacturing a new genetically engineered organism. (A MCAN submission would also be required for a significant new use of an existing genetically engineered microorganism.) EPA requires the submitter to include "all information known or reasonably ascertainable by that person that would permit EPA to make a reasoned evaluation of the health and environmental effects of the microorganism, or any microbial mixture or article, including information on its effects on humans, animals, plants, and other microorganisms, and in the environment." The regulation specifies certain information to be submitted to the extent it is known or reasonably ascertainable by the submitter, including a description of the recipient microorganism, genetic construction of the new organism, phenotype and ecological characteristics, by-products, total production volume, use information, worker exposure and environmental release information and any test data in the possession of the submitter relating to health and environmental effects (40 C.F.R. §725.155 and 40 C.F.R. §725.160). EPA has 90 days from the date

of the receipt of the MCAN to determine, on the basis of the information submitted, whether the genetically engineered microorganism would pose an "unreasonable risk" and to require any controls to protect against such a risk.

The application of EPA's rules to synthetic microorganisms raises several issues. First, as noted previously, EPA's definition of "intergeneric microorganism" may not cover some synthetic microorganisms. More significant, however, is the lack of information needed by EPA to confidently assess risks of complex synthetic microorganisms. Much of the information required to be included in the MCAN, such as ecological characteristics of the organism, may be difficult to provide in cases where a complex organism has been assembled from multiple sources.

Moreover, this dilemma illustrates one of the well-known fundamental weaknesses of TSCA; namely, TSCA does not require developers to test new chemicals for potential toxicity, pathogenicity or other harmful effects. Rather, it simply requires the developer to provide EPA with such information relevant to EPA's risk assessment as it has in its possession or may be "reasonably ascertainable." Only about one-third of all of the pre-manufacturing notices received by EPA include any test data on the chemical properties, and of those, only about 15% include any data on health effects (Schierow, 2007). In the absence of such information, EPA has assessed risks using databases and models for estimating potential human health and environmental effects that compare the new chemical's molecular structure with structures of chemicals with known harmful properties. Some commentators have argued that there is not a lot of empirical basis for EPA's models, and they may not be very accurate (Davies, 2007).

Under TSCA, EPA has to rely on the manufacturer to voluntarily provide the data the agency needs to assess risks; it is difficult to compel it. Section 5(e) of TSCA provides that, if EPA lacks information to permit a "reasoned evaluation" of the health and environmental effects of the chemical, it may delay or prohibit its manufacture only if it can show that the chemical "may present an unreasonable risk"—a catch-22 requirement, since the agency cannot make the finding of "unreasonable risk" without the data that it does not have.

In practice, EPA's experience with genetically engineered microorganisms under the MCAN process is limited. In the last 10 years, EPA has reported receiving only 16 MCANs; EPA's Web site does not list the number of certifications indicating an exemption from the MCAN requirements (U.S. Environmental Protection Agency, 2007). As a result, it is difficult to assess the effect of EPA's TSCA program. Nevertheless, no adverse events have been reported in association with the use of genetically engineered microorganisms in contained production facilities, despite their widespread use.

For complex synthetic microorganisms used in a strictly controlled production process facility, the lack of information to assess risk may not be so critical if EPA can be confident that adequate containment and other control measures are in place to prevent an accidental release. However, it begs the question of how EPA can determine what the appropriate level of containment is. Manufacturers are unlikely to be interested in producing chemicals under very high and costly biosafety confinement conditions. But EPA is also unlikely to exempt complex synthetic microorganisms from the MCAN requirements.

c. Conclusions Regarding Synthetic Microorganisms in a Contained Industrial Processing Facility

Both FDA and EPA have the authority under the FDCA and TSCA, respectively, to regulate the process of using synthetic microorganisms to produce drugs or other industrial chemicals in a contained production facility to ensure safety, including protection of workers, public health and the environment. However, both agencies will face challenges in assessing the risks of complex synthetic microorganisms and determining the appropriate levels of containment and biosafety controls required. First-generation synthetic microorganisms may not differ appreciably from the current generation of genetically engineered microorganisms, and would not present any regulatory issues. But as synthetic biology enables the construction of complex new microorganisms, the assessment of their risk is likely to become more challenging.

Since FDA must approve any new manufacturing process for a drug, it has the power to require a manufacturer to produce the testing and evidence to provide a basis for FDA's risk assessment. (If the manufacturer cannot demonstrate safety, FDA has the power to prevent the manufacturer from marketing the drug.) In contrast, EPA cannot compel a manufacturer to test or develop new information; the manufacturer need provide only the information in its possession or that is "easily accessible." Under those circumstances, it is unclear how EPA would make any determination of risk since there would be no validated models or databases that it could use to compare the synthetic microorganism to other organisms with known risk characteristics. Under TSCA, unless EPA can find that the new chemical substance would pose an unreasonable risk, the product may move to market.

3. Intended Environmental Releases of Synthetic Microorganisms

Finally, synthetic microorganisms may be developed for applications that involve uses outside of a contained facility. One example would be a final product—such as a drug or medical device—that would consist of a synthetic microorganism, or include a synthetic microorganism as a component. Testing a drug on animals and humans would also constitute a non-contained use, since it involves intentional exposure to humans or animals being tested. Other examples would include final products containing synthetic microorganisms intended for direct use in the environment, such as pesticides, disinfectants or bioremediation tools. It would also include the use of microorganisms in a non-contained industrial production facility, where production of chemicals on a larger scale may require the use of fermentation ponds rather than closed bioreactors or fermentation vessels. Finally, it would also cover field trials and other non-contained testing of a product consisting of or containing a synthetic microorganism.

Intentional non-contained use shifts the relevant risk issues to the potential for harm to public health and the environment before the synthetic microorganism is tested in a non-contained setting or before it is used in a final product intended for sale and distribution.

a. Drugs, Biologics and Medical Devices under the FDCA

Under the FDCA, no drug, biologic or medical device may be sold in commerce without a prior approval from the FDA finding that it is safe and effective; the burden of proof on these issues rests with the developer. In addition, prior FDA approval is needed for any clinical trials that involve intentional exposure or testing on animals and humans. As a result, FDA is in a strong position to require the developer to test and to provide information the FDA needs to make a safety assessment during the drug development, testing and approval process. FDA's safety assessment focuses primarily on ensuring that a drug or other biomedical product can be safely used on humans for the purposes for which it was designed. Typically, the FDA requires clinical trials to prove safety and efficacy. However, as part of its safety assessment, FDA may also look more broadly to ensure that the product can be used in a manner that does not harm other organisms or the environment.[36] In addition, the submission of an investigational new drug approval or a new drug approval requires a concurrent environmental assessment or claim of categorical exclusion from such an assessment.[37]

Using this approach for synthetic biology products under its jurisdiction, FDA has adequate authority to ensure that the developer provides whatever information FDA need to decide whether a product is safe and effective.

b. Industrial Products under TSCA

Under TSCA, EPA also regulates non-contained uses of genetically engineered microorganisms, such as experimental field testing or industrial bioprocessing in non-contained facilities. It also covers the manufacture of final products consisting of or containing genetically engineered microorganisms intended for release into the environment, such as bioremediation, biomass conversion, biosensing and other applications. (Microbial pesticides are regulated under a different law, as noted below.)

Field Testing. EPA's rules allow R&D activities involving intentional testing outside a contained environment under several conditions. EPA has

identified a limited number of genetically engineered microorganisms that may be used under certain circumstances in small-scale field testing without prior EPA approval (40 C.F.R. §725.238). However, for most field trials, the developer must submit a TSCA Experimental Release Application (TERA) at least 60 days prior to initiating field trials. Along with the application, the developer is required to submit "all information known to or reasonably ascertainable" on the proposed R&D activity in the microorganism relevant to EPA's risk assessment (40 C.F.R. § 725.255). EPA rules set out a list of information regarding the microorganism and the proposed field test that should be included, although the information is not as extensive as that required for the MCAN. EPA has 60 days from the date of receipt of the final completed application to review the TERA. EPA approves the field trial if it finds that test would not create "an unreasonable risk of injury to health or the environment." In the last 10 years, EPA has approved 19 TERAs (U.S. Environmental Protection Agency, 2007).

Under TSCA, however, EPA has no authority over non-commercial research. That leaves open the question of whether there is any external oversight for field testing carried out as part of a basic research program. For example, field trials of a synthetic microorganism to gain basic knowledge about survivability, reproduction and spread would be valuable research. At the same time, such research clearly poses the same kind of public health and environmental risk as commercial research does. However, unless the research had some commercial purpose, such as gathering information for a specific product approval, EPA would have no jurisdiction. At the same time, the NIH Guidelines do not address non-contained field testing of genetically engineered microorganisms. It is possible, as suggested below, that no field trial or release could be done without a permit from the Animal and Plant Health Inspection Service (APHIS), but this is an area that needs clarification.

Final Products. For other non-contained uses of genetically engineered microorganisms, such as their use in a final product intended to be sold in commerce or used in the environment, developers are required to submit a MCAN before starting manufacture or production of the product. As noted in the previous section, however, TSCA authority and the MCAN process may not provide EPA the information it needs to make a reasoned risk evaluation of complex synthetic microorganisms. This weakness is likely to be of even greater concern when the agency faces a decision to permit the non-contained use of genetically engineered microorganisms. In a contained-use setting, EPA may place greater reliance upon physical and biological containment as a means to manage risk. In a non-contained use, however, EPA will have to rely more on its judgment about the potential behavior of the microorganism and its interaction in the environment, information that is likely to be incomplete and uncertain for some complex synthetic microorganisms.

c. Microbial Pesticides under the Federal Insecticide, Fungicide and Rodenticide Act

Under the Coordinated Framework, EPA regulates biotechnology products intended for use as pesticides, including microbial pesticides. EPA regulates pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)[38] (7 U.S.C. §136 *et seq.)*. Before a pesticide can be marketed, EPA must find that when used as instructed, the pesticide will "not generally cause unreasonable adverse effects on the environment." The burden is on the developer to provide EPA with sufficient information to make that determination. In addition, EPA has the authority to establish tolerances for pesticide residues in food.

During the research stage, EPA's role is limited to ensuring the safety of experimental field trials of a pesticide. EPA grants "experimental use permits" to developers in order to allow them to collect field data in support of the pesticide-approval process. For conventional chemical pesticides, EPA permits developers to conduct small-scale (under 10 acres) field trials of pesticides without prior EPA approval, provided that certain conditions are met.

As with TSCA, EPA has issued regulations under FIFRA that apply specifically to the

unique issues posed by genetically engineered microorganisms intended for use as pesticides (40 C.F.R. §172.45). Under these regulations, a developer must notify EPA prior to any field trial of a genetically engineered microbial pesticide[39] or for any small-scale tests of a genetically engineered microbial pesticide performed in a facility without adequate containment and inactivation controls. Small-scale tests may be conducted without prior EPA approval in facilities with adequate containment and inactivation controls. In its regulations, EPA states that facilities that comply with the NIH Guidelines meet the requirements for adequate containment and inactivation controls. In the absence of compliance with NIH Guidelines, a facility may still meet the containment and inactivation requirements provided that there are internal approval requirements and records are kept for EPA's inspection.

If the notification is required, EPA requires the submission of specific data to help it assess the potential health and environmental risks associated with the genetically engineered microorganism, including the identity of the microorganism that constitutes the microbial pesticide, the description of the natural habitat of the parental strain of the microbial pesticide, information on the host range of the microbial pesticide and its survival and ability to become established and spread and data on the potential for genetic transfer and exchange with other organisms and the genetic stability of any inserted sequences in the microbial pesticide (40 C.F.R. § 172.48).

FIFRA gives EPA adequate authority over synthetic microorganisms intended to be used as pesticides, but the question remains how EPA will be able to assess their potential environmental risks either for field testing or for final approval. Since the law requires pre-market approval, EPA has broad authority to require the developer to submit data showing that the product would not cause unreasonable risks when used as directed. But depending on the construction of the synthetic microorganism, it may be difficult for developers to provide the kind of information that EPA is requiring in order to make its risk assessment. For example, if the microorganism contains sequences made from scratch or from a variety of naturally occurring sources, data on issues like natural habitat and range, potential for survival and genetic transfer and potential for impacts on non-target organisms may be difficult to provide in advance of actual testing. In such a case, EPA's ability to carry out an informed risk assessment prior to field testing is likely to be limited. Given the limitations of confinement techniques in open field trials, EPA may want to consider limiting initial trials of synthetic microorganisms intended for use as pesticides to contained facilities or require that they be done under strong biological confinement conditions until more experience is gained.

d. Potential Plant and Animal pests under USDA APHIS

USDA's Animal and Plant Health Inspection Service (APHIS) has broad regulatory authority under the Plant Protection Act (7 U.S.C. § 7758(c)) and the Animal Health Protection Act (7 U.S.C. §§ 8303, 8305, and 8306) to protect agricultural animals and crops from diseases and pests. APHIS strictly controls the importation, transportation and use of known animal and plant pathogens and has broad authority to prevent and mitigate the introduction and transmission of animal and plant pests and diseases.

Under the Coordinated Framework for biotechnology products, APHIS has responsibility for reviewing genetically modified plants and organisms—including microorganisms—for potential risks to agriculture and the environment. In particular, APHIS has issued regulations that require developers of most genetically engineered plants and organisms to obtain prior approval for field trials or commercial use (7 C.F.R. Part 340).[40] APHIS regulations apply to genetically engineered microbes if the donor or recipient organism or the vector or vector agent is classified as a plant pest or is an "unclassified organism and/or an organism whose classification is unknown" (7 C.F.R. Part 340.1).[41] Such organisms may not be transported or released into the environment without either a prior notification to or, in some instances, a permit from, APHIS. APHIS allows

many low-risk genetically engineered plants (as defined in its regulations) to be tested in field trials without a permit provided that the developer gives APHIS advance notice (7 C.F.R. Part 340.3 (b)). Most genetically engineered microorganisms, however, would not be eligible for the streamlined notification process, and would therefore be required to obtain a permit from APHIS before being field tested or otherwise released into the environment.

To obtain a permit, APHIS requires the developer to submit information to allow APHIS to conduct an assessment of the organism's potential risk to plants, animals and the environment. The required information includes data on the organism's structure and modifications, and its known harm to other organisms, potential for invasiveness, impacts on biodiversity and threats to plants and animals. APHIS may impose conditions on the field trial or other release in the permit as a means of preventing or mitigating any risk. In some cases, APHIS may be required to prepare an Environmental Impact Statement under NEPA prior to granting a permit.[42]

APHIS has reviewed and approved thousands of notifications, field trial permits and petitions for non-regulated status for genetically engineered plants and microorganisms. By far the most significant problem that has emerged is the difficulty in preventing low-level gene flow of genetically engineered crops. While this has not resulted in any reported harm to the environment or to public health, it has created significant economic issues relating to the responsibility for "cleaning up" unwanted or unapproved gene flow. Despite efforts to minimize gene flow from field trials through biological and physical containment measures, the evidence to date suggests that it is virtually impossible to prevent all gene flow from field trials.[43] While this experience is based primarily on plants, its relevance for microorganisms is evident. Once microorganisms are released into the environment, it is unlikely that they will be able to be completely contained in every field trial. Some escape is almost inevitable, a factor for risk managers to consider (National Research Council, 2005).

Field trials or other non-contained uses of synthetic microorganisms would be covered by APHIS's current regulations under the category of an "unclassified organism and/or an organism whose classification is unknown." A synthetic microorganism would not appear to meet any of the requirements for exemption or for the streamlined notification process, and therefore would require a permit by APHIS before it could be used in a field trial or otherwise released into the environment. Since a synthetic microorganism cannot be field tested without a permit, developers would have the burden to produce the information needed by APHIS to determine whether the organism presents a risk to plants, animals or the environment. In the absence of that information, field testing would not be approved. As noted previously, meeting that burden of proof may be difficult.

e. Conclusions Regarding Non-Contained Uses of Synthetic Microorganisms

If applied to synthetic microorganisms, the product-by-product approach of the biotechnology regulatory framework would provide a patchwork regulatory cover. Field tests of synthetic microorganisms, or their use outside non-contained settings, would likely be reviewed by at least one agency. But the regulatory approaches of those agencies differ. For products under the jurisdiction of the FDA, such as drugs, biologics and medical devices, products that consist of or that contain synthetic microorganisms would be subject to strict scrutiny from development and testing through manufacturing and distribution to ensure safety and biosafety. Field testing or environmental releases of virtually any synthetic microorganism would require an APHIS permit to ensure that it did not pose a risk to plants, animals or the environment, but it is difficult to envision the conditions under which synthetic microorganisms could be field tested without some risk of spreading beyond the field trial site. Nevertheless, as with drug and biomedical applications, the burden is on the developer to provide APHIS with enough information to support the decision that the synthetic microorganism will not be a threat to plants, animals and the environment. APHIS's regulation is therefore likely to be more significant than EPA's

under TSCA, where EPA has little authority to require the development of information needed to support its risk assessment. While APHIS could provide a regulatory backstop to EPA, an important gap is left: APHIS does not have the responsibility (or expertise) to assess potential risks to human health, which is one of the main purposes of TSCA. Thus, outside of products under FDA's jurisdiction, it is unclear how the regulatory process will assess and manage the human-health risks of synthetic microorganisms used in non-contained conditions. Fortunately, it may be some time before such applications are developed, and there will be time to clarify the regulatory process.

Finally, as noted above, the fundamental problem remains the lack of information on which to make a rational risk assessment for complex synthetic microorganisms. Faced with uncertain and inadequate information, regulators can err on the side of caution and refuse to approve the product, possibly forgoing the societal benefit of a valuable new product; that is the regulatory approach embodied in the approach of FDA, APHIS and EPA under the pesticide laws. On the other hand, faced with uncertain and inadequate information, regulators can err on the side of innovation and economic benefit, possibly risking harmful consequences to public health and the environment; that is the regulatory approach embodied in TSCA. Neither approach is likely to be optimal. But without a mechanism to ensure that relevant risk research on complex synthetic microorganisms is undertaken so that agencies can have some informed basis for making a risk assessment, that appears to be the inevitable outcome.[44]

The preceding analysis has focused on whether agencies have sufficient authority under existing laws and regulations to address the potential risks of future microbial synthetic biology products. As a practical matter, however, the question of whether agencies have sufficient resources, including scientific expertise, to carry out their regulatory responsibilities is likely to be just as important as the question of legal authority. Recent reports have raised serious questions about whether agencies have sufficient resources to meet their current responsibilities. For example, a report by the Subcommittee on Science and Technology of the FDA's Science Board concluded that "the science at FDA is in a precarious position: the Agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities" (Subcommittee on Science and Technology, 2007). While an assessment of agency resources and scientific capabilities is beyond the scope of this report, the ability of agencies to respond wisely to emerging and converging technologies such as nanotechnology and synthetic biology will require agencies to develop expertise and capabilities in cutting-edge science.

Finally, the regulatory system assumes that responsible companies and researchers will know about the various regulatory permits and requirements and make good faith efforts to comply. The regulatory system is not designed to deal with bioterrorists or other bad actors who intentionally avoid the regulatory system. In addition, the rise of "garage synthetic biology"raises a similar concern about experiments that may take place outside of institutions with the knowledge and incentives to comply (McKenna, 2009). Unlike other technologies, synthetic biology experiments have few technical or cost barriers. While beyond the scope of this study, any serious effort to ensure biosafety of synthetic biology will need to consider the independent researcher who may have little knowledge about or interest in biosafety or regulatory requirements.

V. Conclusions

Synthetic biology, like other new technologies, poses a challenge for policymakers who must balance the desire for introducing innovative beneficial new products with the need to prevent potential harm to public health or the environment. It is widely assumed that the policies and regulations developed for genetic engineering are an appropriate template for synthetic biology. While the development of biotechnology policy has not been without problems in the United States, for the most part it is viewed as a success: beneficial new products in medicine and agriculture have been introduced without evident harm to public health or the environment.

Concerns about the accidental release of a synthetic microorganism from a contained research environment and the potential public health and environmental impacts of synthetic microorganisms intended for use in non-contained settings are similar to those raised 30 years ago at the beginning of recombinant DNA engineering. To that extent, there appears to be little reason to treat synthetic biology any differently than other genetic engineering technologies. Moreover, the information needed to assess those potential risks would be the same, regardless of the process by which an organism was genetically engineered. But in the case of complex synthetic microorganisms, there is likely to be greater uncertainty about some of the required information because the genetic parts used to assemble the organism may function together in ways that cannot be predicted from their function in their sources. While rDNA research also started in the mid-1970s amidst similar uncertainty about the potential risks, scientists were able to confirm after several years of research that the risks of most genetically engineered microorganisms could be confidently assessed on the basis of knowledge about the host and donor organisms and the vectors used to make the genetic transformations. That may be substantially more difficult for complex synthetic microorganisms that are constructed from artificial genetic segments or from a variety of naturally occurring organisms. First-generation synthetic microorganisms, however, are likely to be simpler applications of the technology and will probably be similar to current microbes engineered through rDNA techniques, thereby posing fewer challenges for regulators.

As a result, even though the existing policy and regulatory framework for biotechnology applies, with minor fixes, to cover synthetic microorganisms, it is far from clear that doing so would provide regulators with any confidence that they were hitting the right balance between over-regulation and under-regulation. The uncertainty about potential health and environmental risks of complex synthetic microorganisms will force policymakers to use default judgments about safety or risk, and outcomes will depend on the statutory framework. For laws that require mandatory pre-market approvals, it will likely prove difficult for industry to meet its burden of proof to show safety, and as a result, potentially beneficial and safe products will be kept off the market. On the other hand, laws that place the burden of showing risk on the agency, such as TSCA, may well under-regulate and allow harmful new products to reach the marketplace. It may develop, as it did with genetic engineering, that several years of research can clearly demonstrate that synthetic microorganisms pose the same low levels of risk as most genetically engineered microbes. Many researchers already believe that this is quite likely; others are less certain.

At this beginning stage of a new technology, how a technology is framed—that is, how it is perceived by the public and the policymakers in relationship to existing and familiar technologies—can play a critical role in the subsequent development of regulatory policies. A technology that is viewed as novel and potentially dangerous is likely to end up with a highly precautionary regulatory policy, while one that is viewed as familiar and safe will be treated no differently than conventional existing technologies. The framing process for synthetic biology is now well underway, and the outcome will depend on the thoughtful engagement of all interested parties.

Endnotes

1. See, e.g., U.S. Department of Agriculture, Animal Plant Health Inspection Service, Proposed Rule: Importation, Interstate Movement, and Release into the Environment of Certain Genetically Engineered Organisms, 73 Fed. Reg. 60008 (October 9, 2008); Department of Health and Human Services, Food and Drug Administration, Notice of Availability, Guidance for Industry: Regulation of Genetically Engineered Animals Containing Heritable rDNA Constructs, 73 Fed. Reg. 54407 (September 19, 2008).

2. Biotechnology critics argue that the lack of apparent harm does not necessarily mean that no harm has occurred, but rather that it simply has not been observed. They point to the lack of food labeling and monitoring, which would make it difficult to trace any subtle or chronic food-safety problem. For example, the contamination of the food supply by low levels of a biotech variety of corn called Starlink, noted in footnote 3, was discovered by a public interest group, not a governmental agency. Some experts have recommended that the federal government should enhance its food safety monitoring program (Institute of Medicine and National Research Council, 2004). In the environmental area, EPA relies upon manufacturers to detect and report adverse events, including any increase in pest resistance to Bt corn, a practice that has also been criticized (Taylor & Tick, 2003).

3. Perhaps the most-publicized problem was the discovery in 2000 that an unapproved variety of genetically engineered corn called StarLink had contaminated the U.S. corn supply at low levels. The discovery led to a voluntary recall of thousands of consumer products containing corn. While EPA had initially declined to approve Starlink for human consumption out of concerns that it could be an allergen, the FDA and Centers for Disease Control and Prevention found no evidence of adverse health consequences resulting from the low level exposures (Taylor & Tick, 2001).

4. At the present time, the largest DNA fragment that can be accurately chemically synthesized is no more than 100 base pairs—small sequences known as oligonucleotides (Garfinkel, Endy, Epstein, & Friedman, 2007). In order to create longer genetic sequences, scientists need to stitch together these smaller oligonucleotides by processes that remain technically complex at the present time. As noted in the text, however, researchers have reported the synthesis of sequences of increasing length, including the synthesis of the genome of *Mycoplasma genitalium*, slightly larger than a half a million base pairs (Holt, 2008).

5. The accelerating convergence of related technologies makes it increasingly difficult to place new technological developments into traditional discipline-based categories, and to some extent the attempt to do so is not particularly useful. For example, scientists at Arizona State University have recently reported being able to use a cell's DNA-replication process to produce copies of a designed DNA nanostructure, illustrating the overlapping paths of synthetic biology and nanotechnology (Ball, 2008). Indeed, as nanotechnology developments provide engineers with greater ability to manipulate materials at the same nanoscale levels as molecular biology, the distinction between the two technologies is likely to disappear.

6. Keasling and his colleagues engineered the yeast to produce artemisinic acid by engineering the mevalonate pathways and introducing several genes from different organisms to direct the cell to produce artemisinic acid.

7. Many of the controversies surrounding rDNA technology have involved decisions relating to intellectual property, including the Supreme Court decision in 1980, *Diamond* v. *Chakrabarty*, 4 47 U.S. 303, that upheld the patenting of modified living organisms. Other controversies include the widespread use of patent protections for genetically engineered seed varieties, and interpretations by the Office of Patents and Trademarks to extend patent protection to various genetic sequences. Concerns have been expressed about the impacts of such decisions on innovation, research and economic competition, as well as their broader ethical, moral, and social implications (see, e.g., Heller & Eisenberg, 1998; Thompson, 1995). As they did with regulation, European nations have taken a more aggressive role than the United States in using intellectual property policies to address the ethical dimensions of new technologies. Synthetic biology will undoubtedly face similar controversies with respect to intellectual property policies and may face similar divergent approaches to governance.

8. Many states have also enacted strict liability laws that impose liability regardless of negligence with respect to certain categories of products.

9. While it is beyond the scope of this paper, it is important to note that framing has cultural and political, as well as scientific, aspects. While science is clearly relevant to the issue, the question of whether a product should be treated the same as or differently than other products is ultimately a policy judgment influenced by political and cultural values. In large part, cultural views towards uncertainty, trust, and risk, are intrinsically involved in decisions about the regulations of new technologies (Jasanoff, 2005). Science alone is not sufficient to resolve the question for policymakers.

10. The first genetically engineered food to be considered by the FDA, the Flavr Savr tomato, was reviewed under a food additive approach at the request of Calgene, its developer. Calgene requested that FDA approve as a food additive the kanamycin antibiotic resistance marker left in the tomato as a result of the genetic engineering process. Calgene conducted many studies and submitted information to FDA; the approval process took several years. Following the Flavr Savr tomato experience, FDA announced its policy to consider genetically engineered foods under a "substantial equivalence" policy approach and a voluntary pre-market consultation process. See: Department of Health and Human Services, Food and Drug Administration, *Statement of Policy: Foods Derived from New Plant Varieties*, 57 Fed. Reg. 22984 (May 29, 1992). Developers of genetically engineered crops intended for use as food or feed routinely consult with the FDA prior to marketing in order to ensure that FDA has no safety concerns. While legally voluntary, the developers argue that, as a practical matter, the consultation process is mandatory since the market would be unlikely to accept a biotechnology crop that had not been through FDA review. In addition, all crops would be subject to mandatory pre-market review for environmental safety by USDA or EPA.

11. In 2004, the President's Science Adviser noted, "While the technologies enabled by atomic scale capabilities are revolutionary, they are not particularly new. Nature has experimented with nanostructures since the earth began to cool four and a half billion years ago …" (Report of the International Dialogue on Responsible Research and Development of Nanotechnology, 2004). In 2008, EPA finally conceded that carbon nanotubes cannot simply be viewed as graphite; sometimes the "new" is in fact new.

12. For the purposes of this paper, a "synthetic microorganism" is a bacterium, virus or other microorganism containing synthetic genetic segments or natural genetic segments from unrelated organisms assembled through synthetic biology techniques.

13. There is a long history of efforts to ensure the safety of workers in research laboratories by developing adequate containment guidelines and other good laboratory practices. In the late 1960s, the U.S. Public Health Service and the USDA developed guidelines for safe laboratory handling of potentially infectious agents. Today, the principal guide to the safety for research using potentially infectious agents is the publication *Biosafety in Microbiological and Biomedical Laboratories* (BMBL), compiled by the Centers for Disease Control and Prevention and the National Institutes of Health. The BMBL Guidelines are considered the state of the art for the handling of infectious and etiological agents of human disease. To the extent that the BMBL guidelines are focused on appropriate containment mechanisms to avoid exposing workers to infectious diseases, they are also effective in preventing the accidental transmission to the public. The NIH rDNA Guidelines and the BMBL biosafety practices are mandatory only through contract provisions contained in federal grants or individual institution requirements. The Occupational Safety and Health Administration enforces regulations intended to protect laboratory and health-care workers from exposure to certain bloodborne pathogens such as HIV and hepatitis virus. More recently, research using certain specified "select agents" that could be used for bioterrorism has also been subject to binding rules and regulations.

14. Known incidents are an explosion at a Soviet bioweapons facility in Sverdlovsk, Russia, in 1979, which exposed the surrounding community to anthrax, killing approximately 100 people, and an accidental smallpox release from an English laboratory in 1978 that killed one person in the community and caused a limited outbreak.

15. While current biosafety practices are likely to be adequate to protect workers and communities from the potentially dangerous research activities, such traditional practices may not be adequate to deal with intentional acts of terrorism and other biosecurity concerns (Graham, B., Talent, J., Graham, A., Cleveland, R., Rademaker, S., Roemer, T., Sherman, W., Sokolski, H., Verma, R. 2008).

16. The StarLink case is discussed at note 2. In 1999, a preliminary study published in *Nature* raised the possibility that the pollen from corn plants genetically modified to express pesticidal proteins from *Bacillus thuringiensis* (*Bt*) could kill Monarch larvae. Subsequent research discounted the possibility, but noted that one variety of *Bt* corn that had been withdrawn from the market for other reasons expressed much higher levels of Bt toxins that were associated with sublethal effects on butterflies (Zangerl, et al., 2001). In 2002, experimental genetically engineered corn designed to produce a protein for a pig vaccine was inadvertently mixed in with soybeans intended for the food market; the mistake was caught before the shipment went to market. The modified corn was not believed to present a food-safety risk (Gillis, 2002).

17. A recent Government Accountability Office report highlighted the failure of the regulatory system to prevent low-level accidental mixing of unapproved varieties of genetically modified crops and seeds (Government Accountability Office, 2008). Preventing gene flow from microorganisms, plants and animals is difficult (National Research Council, 2005). Experience with genetically engineered crops suggests that 100% confinement for open-pollinated crops such as corn may be impossible

to achieve. Despite a ban, traces of a genetically modified corn gene were reported in native land races in remote regions of Mexico (Commission on Environmental Cooperation, 2004). There have been several other instances where unapproved "events" (rDNA genetic transformations) were found to have become mixed with food supplies, none of which posed any public health threat. In 2006, rice farmers found widespread low-level contamination of their rice seed with an unapproved genetically engineered variety, causing rice farmers an estimated $150 million in damages and temporarily stopping U.S. exports (Lee, 2006). Organic growers have also suffered damages from unwanted gene flow from biotech crops, and California recently enacted legislation addressing grower liability.

18. In 2002, the White House Office of Science and Technology acknowledged this point and stated, "As the number and diversity of field tests increase, the likelihood that cross-pollination due to pollen drift from field tests to commercial fields and commingling of seeds produced under field tests with commercial seeds or grain may also increase. This could result in intermittent, low levels of biotechnology-derived genes, and gene products occurring in commerce that have not gone through all applicable regulatory reviews" (Office of Science and Technology Policy, *Proposed Federal Actions To Update Field Test Requirements for Biotechnology Derived Plants and To Establish Early Food Safety Assessments for New Proteins Produced by Such Plants*, 67 Fed. Reg. 50578 [August 2, 2002]).

19. Genetic engineering can lead to unexpected results. In one well-publicized published case involving a well-known pathogen, researchers genetically engineered a mousepox virus using rDNA technology to express interleukin-4 with the goal of creating infertile mice. The modification had the unexpected result of increasing the virulence of the mousepox virus, enabling it to kill mice that had previously been immunized against mousepox (Jackson, Ramsay, Christensen, Beaton, Hall, & Ramsaw, 2001).

20. NIH Guidelines for Research Involving Recombinant DNA Molecules, 59 Fed. Reg. 34496 (July 5, 1994), as amended. While the NIH Guidelines on their face apply only to NIH-funded research or institutions, other federal science funding agencies, including the National Science Foundation, the Department of Energy and the Department of Defense, have incorporated the NIH Guidelines by reference in their own grants. As a result, any federally funded research involving rDNA molecules would be required as a condition of the grant to comply with the NIH Guidelines. Human gene therapy experiments are one of the few areas in which the RAC is still active in reviewing proposed experiments.

21. NIH approval of a proposed field trial of a genetically modified microorganism intended to reduce frost damage in strawberry fields was halted by a court ruling that NIH had failed to conduct an adequate environmental assessment as required by the National Environmental Policy Act. *Foundation for Economic Trends* v. *Heckler*, 587 F. Supp. 753 (D.D.C. 1984), vacated in part, 756 F.2d 143 (D.C. Cir. 1985). With the commercialization of biotechnology around the corner, the Reagan administration realized that NIH's rules would not apply to privately funded research and that clearer regulation was needed.

22. Promoters of new legislation argued that a new law would have several benefits. First, new laws tend to lead toward increased resources for agencies to implement them. This benefit can be significant in the typical resource-constrained world of regulatory agencies. In addition, a new law could be tailored to the issues presented by biotechnology, rather than stretch old laws to reach new technologies. While a new law could theoretically hit the "sweet spot" of regulation, the vagaries of the legislative process and politics suggest that such an outcome is improbable. In addition, new legislation creates significant uncertainty and delay while regulatory agencies translate broad and vague legislative language into specific regulatory proposals.

23. While the focus of this paper is federal laws and regulations, it should be noted that states and localities have legal authority to enact laws and regulations to protect their citizens, subject to certain Constitutional limitations. The town of Cambridge, Massachusetts, adopted the first ordinance dealing with biotechnology research in 1976, and both Berkeley, California, and Cambridge, Massachusetts, have adopted notification requirements for nanotechnology research.

24. In 2002, Congress passed the Public Health Security and Bioterrorism Preparedness and Response Act, which required institutions, including research labs at universities, to notify the U.S. Department of Health and Human Services and the U.S. Department of Agriculture of the possession of certain specified pathogens and toxins (called "select agents") or certain animal or plant pathogens or toxins identified by the USDA.

25. The NSABB was established to review government policy relating to bioterrorism and select agents. In December 2006, the NSABB expressed concern that current biosafety guidelines did not provide adequate guidance for synthetic biology research (National Science Advisory Board for Biosecurity, 2006).

26. With some minor modifications from the RAC-adopted version, the NIH published the proposed revisions for public comment on March 4, 2009. 74 Fed. Reg. 9411 (March 4, 2009).

27. Some of the weaknesses of the NIH Guidelines in ensuring compliance became clear in 1999, following the death of a patient in a clinical trial of human gene trial therapy (Rainsbury, 2000).

28. A number of specific product categories are exempted from TSCA because they are regulated by another law, including pesticides, tobacco, nuclear material, alcohol, and food, drugs, cosmetics and devices regulated under the FDCA (15 U.S.C. §2602(2)(A)).

29. TSCA defines "chemical substances" as "any organic or inorganic substance of a particular molecular identity, including—(i) any combination of such substances occurring in whole or in part as result of a chemical reaction or occurring in nature, and (ii) any element or uncombined radical" (15 U.S.C. §2602(2)(A)).

30. 40 C.F.R. § 700, 720, 721, 723 and 725, Microbial Products of Biotechnology. Since TSCA exempts chemicals otherwise regulated, EPA's rules do not cover genetically engineered microbial pesticides, human or animal drugs or diagnostics or food additives.

31. This interpretation, first forwarded in 1984 when EPA claimed jurisdiction over genetically modified microorganisms, has been criticized by legal scholars, but has not been challenged in court. The effect of the interpretation is to broaden the scope of TSCA to include all living organisms not otherwise exempt from TSCA, although to date EPA has asserted its authority only over microorganisms (Pew Initiative on Food and Biotechnology, 2004).

32. 40 C.F.R. § 725.3. The definition also includes a microorganism that contains a mobile genetic element that was first identified in a microorganism in a genus different from the recipient microorganism. The rules do not include a microorganism that contains introduced genetic material consisting of only well-characterized, non-coding regulatory regions from another genus.

33. The EPA regulations set out a number of indicators for determining whether a researcher not funded directly by a commercial entity "intends to obtain an immediate or eventual commercial advantage," including whether (1) the research is directed toward developing a commercially viable improvement of product already on the market, (2) the researcher has sought or is seeking commercial funding for the purpose of developing a commercial application, (3) the researcher or university has sought or is seeking a patent to protect commercial application which the research is developing, or (4) there is other evidence that the researcher is aware of a commercial application for the research and has directed the research toward developing that application (40 C.F.R. § 725.205(b)(2).

34. A structure is defined in 40 C.F.R. §725.3 as "a building or vessel which effectively surrounds and encloses the microorganism and includes features designed to restrict the microorganism from leaving."

35. EPA lists 10 varieties of microorganisms that are exempt from the TSCA notification requirements, provided also that the introduced genetic material is limited in size, well characterized, poorly mobilizable and free of certain sequences, and that the microorganism must be used in a facility that meets specified physical containment and control technologies. In addition, if the manufacturer does not meet the strict physical containment measures set out in the exemption, it may request a "Tier II" exemption by demonstrating to the agency that there are adequate containment and other controls in place to prevent an unreasonable risk to the environment (40 C.F.R. § 725.428).

36. The FDA has interpreted its "safety" authority to include environmental effects that may pose risks to the health of humans or animals and may deny approval of a product if such risks cannot be mitigated. In the past, the FDA has evaluated environmental safety and required data and information with regard to risks from manufacturing processes, such as occupational exposures or emissions from a manufacturing facility. One example of the agency's use of this authority with respect to biotechnology products is its approval of the recombinant animal drug rBST, where the agency required the developer to submit information on the environmental impacts of rBST, and eventually decided to impose labeling restrictions and specific requirements with regard to syringe disposal.

37. This requirement is derived from the National Environmental Policy Act (NEPA), which requires most federal agencies to review the environmental impacts of any major federal action "such as permit decisions" that could have a significant impact on the environment (42 U.S.C. §§4321-4347). (EPA is largely exempt from NEPA's procedural requirements.) Agencies typically conduct an environmental assessment to determine whether a proposed action would have a "significant impact." (They can also exempt categories of actions through rulemaking that the agency has found to have no significant impact.) If the agency makes a finding of "no significant impact," the decision may move ahead. Otherwise, it is required to conduct a more elaborate Environmental Impact Statement with an opportunity for public comment. NEPA is a procedural law; it does not require agencies to take the action with the least adverse environmental impacts.

38. EPA's definition of "pesticide" is a functional one: "any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest."

39. The EPA regulations cover small-scale testing of microbial pesticides whose "pesticidal properties have been imparted or enhanced by the introduction of genetic material that has been deliberately modified" (40 C.F.R. 172.45(c)(1)), but excludes "microbial pesticides resulting from deletions or rearrangements within a single genome that are brought about by the introduction of genetic material that has been deliberately modified" (40 C.F.R. 172.45(d)(1)).

40. APHIS has recently published proposed new regulations and initiated a public comment period (USDA, APHIS, 2008). The discussion in the text is based on APHIS's current practices. It is worth noting, however, that USDA's proposed rules would continue to cover genetically engineered microorganisms that pose an "unknown" plant-pest risk.

41. APHIS exempts "recipient microorganisms which are not plant pests and which have resulted from the addition of genetic material from a donor organism where the material is well-characterized and contains only non-coding regulatory regions" (7 C.F.R. part 340.1).

42. *International Center for Technology Assessment, et al.* v. *Johanns,* 473 F. Supp. 2d 9 (D.D.C. 2007).

43. See notes 18 and 19, *supra*. Pollen blown by wind or carried by birds or insects can travel for miles (Watrud, et al., 2004). Gene flow can also occur through the horizontal transmission of genes to related organisms in the environment (Bergthorsson, Adams, Thomason, & Palmer, 2003; National Research Council, 2005).

44. While much of the information needed to assess the risk of a genetically engineered organism must be specific to the particular organism, generic research on predicting function from genetic structure and sequences could enhance regulatory confidence in risk assessment.

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One Woodrow Wilson Plaza
1300 Pennsylvania Ave., N.W.
Washington, DC 20004-3027
T 202/691/4000
F 202/691/4001
www.synbioproject.org

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