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BIOTECHNOLOGY 2016

ABSTRACT: The 2016 Biotechnology Industry Seminar reviewed three broad areas where new policies and laws will be needed in the next five to ten years to maximize the promising new technologies emerging from the biotechnology industry. These three areas – "feelings," or the ethics of biotechnology; "framework," or the regulatory environment in which the industry operates; and "funding," the various mechanisms by which biotechnology innovators can resource their ideas – have not kept pace with the rapid changes in technology in the industry. If not addressed, this gap between policy and technology threatens to impede progress or to weaken the United States' competitive advantage in biotechnology.

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PLACES VISITED

Domestic:

California
Amyris Biotechnologies, Inc. (Emeryville, CA)
Arcadia Biosciences, Inc. (Davis, CA)
BioCurious (Sunnyville, CA)
Bolt Threads, Inc. (Emeryville, CA)
Joint BioEnergy Institute (Emeryville, CA)
Monsanto Company (Woodland, CA)
Sandia National Laboratories (Livermore, CA)
Stanford University Center for International Security and Cooperation (Stanford, CA)
Transcriptic, Inc. (Menlo Park, CA)
University of California, Davis, Seed Biotechnology Center (Davis, CA)

District of Columbia
Biotechnology Industry Organization (Washington, DC)

Maryland
Frederick National Laboratory for Cancer Research (Frederick, MD)
Joint Project Manager Medical Countermeasure Systems (Fort Detrick, MD)
Montgomery College (Germantown, MD)
National Institutes of Health (Bethesda, MD)
U.S. Army Medical Material Development Activity (Fort Detrick, MD)
U.S. Food and Drug Administration (Silver Spring, MD)

Massachusetts
Broad Institute of Massachusetts Institute of Technology & Harvard University (Cambridge, MA)
Harvard Stem Cell Institute Boston Children's Hospital, (Boston, MA)
Massachusetts Biotechnology Council (Cambridge, MA)
Massachusetts Institute of Technology Lincoln Laboratory (Lexington, MA)
Scholar Rock Corporation (Cambridge, MA)
Visterra, Inc. (Cambridge, MA)

North Carolina
Almac Diagnostics (Durham, NC)
Bayer CropScience AG (Research Triangle Park, NC)
Biogen, Inc. (Research Triangle Park, NC)
Medicago, Inc. USA (Durham, NC)
North Carolina Biotechnology Center (Durham, NC)
NC State University BioManufacturing Training & Education Center (Raleigh, NC)
Precision BioSciences (Durham, NC)
Syngenta (Research Triangle Park, NC)

International:

Malaysia
Malaysian Biotechnology Information Centre (MABIC)
Ministry of Science, Technology and Innovation (MOSTI)
Sime Darby R&D Facility
U.S. Embassy, Kuala Lumpur

Singapore
Agency for Science Technology and Research (A*STAR)
A*STAR Biomedical Research Council (BMRC)
Bio-Rad Laboratories, Inc.
Johnson & Johnson Asia Pacific
Medtronic International, Ltd.
U.S. Embassy, Singapore

Executive Summary

Biotechnology employs biological systems or living organisms to produce new drugs, uses stem cells to regenerate damaged tissue or regrow an entire organ, produces new chemicals for industry or fuels for vehicles, develops pest-resistant grains, and accelerates the evolution of disease-resistant animals. Biotechnology, or biotech, is poised to become the indispensable industry to human advancement over the next 20 years. In that time, advances in biotech are virtually guaranteed to have a significant and lasting impact on everyone. In each of the industry's major sectors – Agricultural, Industrial and Environmental, and Medical and Healthcare – significant innovations are around the corner.

Building from an overview of the foundations of the industry, centered on the sectors above, this analysis will consider what it takes to succeed in biotechnology: adaptation, risk and innovation, management and personnel, timing, location and last but not least, financing. It also explores biotechnology's link with the *National Security Strategy*. All of these things need to come together to make a long-term, sustainable, and profitable biotechnology industry.

We discussed these issues in meetings and research visits with experts throughout the *Triple Helix* – government, academia, and industry. We determined that the nexus for change is centered around three policy focus areas, which, if not addressed, will eventually stall the industry's rise or lead to crisis as the advances enabled by biotechnology are introduced into a world that is not ready to receive them. These three areas are **feelings**, the ethical questions raised by the biotechnology industry; the regulatory **framework** that provides structure and oversight to the industry; and **funding**.

Thanks to recent technological breakthroughs, three foundational areas of biotechnology, *feeding (agricultural biotech)*, *healing (medical biotech)*, and *fueling (industrial biotech)* are at the cusp of revolutionizing the human experience over the next twenty years. The innovative promises of biotechnology will not just revolutionize our economy, but will also be a key consideration for our continued national security. However, we must consider and apply lessons learned from the recent information technology revolution. The ethical framework, regulatory framework, and resourcing mechanisms for biotechnology have fallen behind the technology's advance, and if these areas are not addressed with updated guidance, regulation and legislation, the U.S. biotechnology sector will suffer. Our seminar derived a series of recommendations to address identified policy gaps.

PART I – SETTING THE STAGE

INTRODUCTION

The biotechnology industry is in the midst of a revolution. Groundbreaking technologies in the headlines, like CRISPR/Cas-9, can produce products—including medicine, food, fuel, and clothing—spanning the entire gamut of human need. Biotech is poised to become indispensable to human advancement over the next twenty years. In that time, advances in biotech will have significant and lasting impact on everyone. In April, the *Washington Post* described these new possibilities:

> With the advent of synthetic biology and gene editing tools, there are amazing breakthroughs being made in medicine, energy and food. Within a few years, we will see cures for debilitating diseases, new biofuels, and grains that can be grown in extreme climates. We will also have many new nightmares: bioterrorism and well-meaning experiments that get out of hand. Imagine a superbug that can cure —or kill—millions of people or a virus which targets one person, say, a U.S. president. This is not science fiction; it is happening.[1]

A number of potentially life-altering technologies are poised to be available in the next five years. Scientists are tantalizingly close to deciphering the link between genes and diseases as varied as schizophrenia and breast cancer. New drugs that treat specific cancer causing genetic mutations are already available on the market, and precision therapies that can repair these mutations before they induce symptoms are just over the horizon.[2] Oxitec LLC has designed a mosquito with a "self-limiting gene" that produces sterile offspring, allowing for the culling of mosquito populations to combat threats like Zika without using noxious pesticides.[3] Newly designed foods like non-browning mushrooms[4] and the genetically modified AquAdvantage salmon, which grows to market size much more quickly than conventional fish,[5] have recently been approved for consumption and offer the potential to produce nutritious foods more cheaply for a growing population. Industrialists have recently begun using biotech to produce fuel, fragrances and even pharmaceuticals from simple baker's yeast.[6]

Unfortunately, these technologies also pose potential dangers. From rogue states to terrorist organizations to biohackers working out of a garage, the power of this technology in the wrong hands could have calamitous results. Potential biotech creations include super viruses, food-borne toxins, or drug-resistant bacteria. Human germ-line editing – in the search of bigger, faster, stronger soldiers, for instance – could fundamentally change what being human means. Even in beneficent hands, a technology like the genetically altered mosquito could lead to downstream changes in the ecosystem that are not fully understood.

Biotechnology is at an inflection point. Although our review begins with the state of the industry and its major sectors -- Heal, Feed and Fuel – our group wanted to investigate more deeply several areas requiring significant policy revision. In our view, to maximize the benefits of these exciting new technologies while safeguarding against potential areas of misuse, three broad areas will require significant policy work in the coming years, and the sooner the better. We have labeled them "feelings," which broadly covers ethical and public perception considerations; "framework," which is the regulatory environment in which biotechnology falls; and "funding," which will examine the mechanisms by which entrepreneurs and biotechnologists can finance and commercialize their inventions.

Part I of this paper provides a short history of biotechnology and an overview of the industry,

a review of the pertinent characteristics of successful biotechnology firms, and a discussion of biotechnology's place within the National Security Strategy. Part II analyzes the "feelings, framework, and funding" considerations that policy makers will need to address in the coming years. Finally, we provide recommendations for policy makers to consider.

A SHORT HISTORY OF BIOTECHNOLOGY

The U.S. Congress' Office of Technology Assessment defined biotechnology as "any technique that uses living organisms or their products to make or modify a product, to improve plants or animals, or to develop microorganisms for specific uses."[7]

Humans have manipulated plants and animals to improve lives and solve problems for thousands of years. The first biotechnologists – the Chinese, Babylonians, Egyptians, and Romans – developed species of animals and plants that improved their nutrition and lifestyle by cross breeding or cross pollination. In modern times, biotechnology has expanded into a number of different areas, all using highly innovative and cutting edge technologies. A growing and vital global industry, biotechnology employs organisms to produce new drugs, uses stem cells to regenerate damaged human tissue or regrow an entire organ, produces new chemicals for industry or fuels for vehicles, develops pest-resistant grains, or accelerates the evolution of disease-resistant animals.

Karl Ereky, a Hungarian engineer, first used the term "biotechnology" in 1919, defined at that time as "all lines of work by which products are produced from raw materials with the aid of living organisms."[8] Twentieth century biotechnology experienced an exponential advancement in scientists' understanding of genetics, microbiology, cell biology, embryology, and molecular biology. The advancements in products that resulted from these discoveries spanned all industries, from fermentation processes that refine starch into paint solvents and acetone used on automobiles to intense research into cellular biology and genetics that led to a number of new discoveries about the relationship of genes and the proteins they code. Scientific and medical discoveries during World War II, like penicillin, energized the pharmaceutical industry. James Watson and Francis Crick's 1953 discovery of the double helix structure of Deoxyribonucleic Acid (DNA) led to many other researchers exploring the expression and decoding of genetic information. Modern molecular biology and biotechnology came into its own during the 1980s and 1990s, when numerous scientists were working toward mapping and sequencing the human genome.

The HIV/AIDS epidemic that started in the late 20th century led researchers to redouble their efforts in biotechnology to seek treatments or a cure through improved biotechnology tools, pharmaceutical drugs, and tests. This focused effort paid unexpected dividends in 1997 with the successful cloning of an adult sheep named Dolly. It was also instrumental in developing the technology that allowed Craig Venter's sequencing of the human genome in 2000, and his institute's unprecedented demonstration in 2010 that a synthetic genome could replicate autonomously – the closest humans have come to creating artificial life.[9]

In the past five years, the pace of innovation has further quickened. Discoveries like CRISPR/Cas-9, innovative solutions like algal biofuels, and the continued advancement of the agricultural industry in genetically modified crops have accelerated and left the world on the precipice of a revolutionary era full of both promise and peril.

Biotechnology in the 21st century will play an important role in U.S. national security. Significant innovations are around the corner in all segments of the industry. Products that feed the hungry, use less and cleaner energy, reduce environmental damage, are produced with more efficient, safer, and cleaner industrial manufacturing processes, or combat debilitating and rare diseases, can all improve our national security. The risks inherent in these developments, through bioterrorism, dual use technologies, or inadvertent and wide-ranging impacts of scientific discoveries, also pose potential threats to national security.

THE U.S. BIOECONOMY – AN OVERVIEW[10]

The U.S. bioeconomy—the economic activity derived from using biotechnology in various applications and industries—is a robust part of overall economic growth in America. Viewed in aggregate, revenue for biotechnology products overall in 2015 was $108 billion, with a $9 billion profit.[11] The category encompasses over two thousand businesses and is anticipated to have a growth rate of 8.3 percent between 2015 and 2020.[12] However, biotechnology is not a single industry; as the U.S. Office of Technological Assessment wrote before it was disbanded in the early 1990s, "biotechnology is not an industry, but a set of technologies that can potentially be used by many industries."[13] Fundamentally, it is a set of tools or processes that scientists use to manipulate organisms and businesses use to build products based on those scientific methods.

These many industries span the entire U.S. economy (see Figure 3), but their products broadly fall into three major categories. Medical biotechnology ("Healing"),which produces biological pharmaceuticals that encompass "a wide range of medicinal products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues and recombinant therapeutic proteins,"[14] is the largest group of products for biotechnology, constituting almost 66 percent of all biotechnology applications.[15] Agricultural applications of biotechnology ("Feeding"), which includes modifying crops to increase drought or pest resistance, constitute the second largest category, with almost 13 percent of applications.[16] The third segment, industrial applications ("Fueling"), includes producing complex molecules like fuel or fragrances from biological processes, and comprises nine percent of applications.

The markets for these products are varied as well. Small biotechnology companies generally sell their products either to pharmaceutical manufacturers or to agricultural companies that sell crop seeds to farmers, with a smaller market for industrial applications.[17] These larger conglomerates with household names like Johnson & Johnson, Merck, Bayer, and Monsanto, then sell end products of biotechnology through complex distribution channels that vary by industry. A more detailed description of each of the three largest sectors of biotechnology follows.

Medical Biotechnology – "Heal"

Medical biotechnology, the largest of the three market segments in biotechnology, is helping to heal the world by using the human genome to guide research. The goals include reducing rates of infectious disease and serious, life-threatening conditions affecting millions around the world; tailoring treatments to individuals to minimize health risks and side effects; and creating more precise tools for disease detection – with the ultimate goal of saving and improving lives.

The United States leads the world in research, commercialization and manufacturing of biopharmaceuticals. Medical biotechnology is a major element of the U.S. economy, and generates huge profits for the many companies that compete in the market. In 2011, medical biotechnology directly and indirectly supported over 3.4 million jobs in the United States, accounted for $789

billion in output (2.9% of total U.S. output), and generated more than $40 billion in federal, state, and local personal tax revenues.[18]

Agricultural Biotechnology – "Feed"

The agricultural industry is one of the nation's largest industries, and biotechnology plays an important role there. "Agricultural applications of biotechnology have helped create a more sustainable food supply by increasing crop yield, reducing agriculture's environmental impact, and enhancing plant resistance,"[19] as seen in insect-resistant crops resulting in "healthier plants and increased food, feed, and fuel stocks while reducing the need for insecticide applications."[20]

However, there remains "significant distrust among U.S. consumers toward biotechnology"[21] and genetically modified organisms (GMOs). Despite the benefits of biotechnology, "well-informed consumers are willing to pay a premium to avoid certain genetically modified foods."[22] This is a concern for bioeconomy stakeholders. "Very intelligent people in science, government, industry, and consumer groups appeared to have determined the best marketing (regarding GMOs) is none at all,"[23] an issue which is covered in greater detail in the "Feelings" section of this report.

Industrial Biotechnology – "Fuel"

Biofuels are an essential long-term innovation needed to address the geopolitical and economic problems stemming from American dependence on foreign oil. Achieving energy independence will benefit U.S. national security and economic prosperity. A 2009 RAND study estimated it cost the U.S. armed forces between $67.5 billion and $83 billion annually to defend oil producing areas and oil shipment routes.[24] If the United States is on the cutting edge of new energy technology, it could be a major boost to Gross Domestic Product (GDP) in the long run – global energy demand is increasing, which will provide opportunities for U.S. energy companies. Reduced reliance on fossil fuels will shield American consumers from global price swings caused by instability in oil producing regions and rising demand in the developing world. If Americans are spending less on energy, they can spend more on other things that increase U.S. GDP.

INDUSTRY OVERVIEW: WHAT DOES IT TAKE TO SUCCEED?

Based on our seminar's research, as well as the interactions we had with numerous executive teams from both start-ups and established companies, the most successful global biotechnology companies share several characteristics that enable them to thrive in a highly competitive market. These include a tolerance for risk and a desire to innovate, the ability and willingness to adapt, extremely talented management and personnel, the right timing and location, and sufficient financing. All of these things combine to make a long-term, sustainable, and profitable biotechnology firm.[25]

Risk Tolerance and Innovation

The biotechnology industry rewards risk and innovation. New products and technologies are the industry's lifeblood, and those firms best at developing innovative techniques or products thrive. The flip side is that start-ups fail often, and it is the willingness of venture capitalists and other funding sources to accept those failures as the price of innovation that allows the industry to continue to afford to test numerous ideas that fail for every success that becomes a product. In the seminar's overseas travels, we noted that tolerance of risk and the resulting innovation is a major U.S. competitive advantage over other countries' biotechnology sectors.

Adaptation

The most successful biotechnology companies adapt quickly to changing market forces and consumer needs. Those that have existed over the long-term have incorporated strategic review processes into their business practices that allow them to adapt or evolve their business model to the changing market. They invest heavily in research and development (R&D) to leverage new technology.

Management and Personnel

A good biotechnology management team clearly communicates the company's values, visions, commitment and culture. Along with proper training and education relevant to the business sector, the most successful management teams we observed all displayed entrepreneurialism, and high levels of motivation, flexibility, determination, commitment, and energy. Although science is the foundation of the biotech company, the management team's ability to visualize and communicate the relationship between the underlying technology and its potential for commercialization portends success.[26]

Timing

Successful biotech companies take a macro view and work hard to predict how the industry (or a particular sector) will develop in the next 5-10 years. The biotechnology industry changes rapidly, as seen by the huge bloom of new product ideas after the introduction of CRISPR/Cas-9. Having multiple products at various stages of development often allows the rapid utilization of new technologies.

Location

Location is a key component of the success of a biotechnology company.[27] Start-ups must consider "the availability and costs of the workforce, realizing that it must be in close proximity to innovative science and markets,"[28] including management and support services. The industry tends to cluster in small areas rich with talent and ancillary support services. In a 2011 speech, President Obama remarked, "When you get a group of people together, and industries together, and institutions like universities together around particular industries, then the synergies that develop from all those different facets coming together can make the whole greater than the sum of its parts."[29] In biotech, clustering draws world-class talent into close proximity, allowing cross-pollination of information and enabling a synergistic relationship between academia, industry, and in the case of pharmaceuticals, hospitals.

Biotech clusters in the United States have developed in the San Francisco Bay area, Durham/Raleigh, North Carolina, and the Boston/Cambridge, Massachusetts area. In Europe, there are clusters in Oxford, Cambridge and London; Basel/Zurich, Switzerland; and Munich/Martinsried, Germany. A significant ingredient in the success of these clusters is their ties with nearby colleges, universities, and hospital complexes: Harvard and MIT in Boston; Duke and North Carolina State in Durham; Stanford and the University of California Davis in San Francisco; and Oxford and Cambridge in the UK. These ties link industry with academia, the home of biotech basic research. Location is also critical for companies as they consider their ability to commercialize their ideas. Clustering of biotech companies enables easier transition of personnel, intellectual property, and equipment (especially in the case of mergers and acquisitions), and offers close contact with the venture capital firms that provide early stage money for these firms. The U.S. *National Bioeconomy Blueprint*, released in 2012, identified these partnerships as integral to the health and growth of the

biotechnology industry, but the document lacked an illustrative plan to help other states create such a cluster.

Financing

Research and development in the biotechnology industry is capital intensive; financing is a huge concern, especially to new startup companies. Additionally, products typically take years or decades to develop, which means start-ups generally cannot expect to make a profit for many years. The Funding section of this report details issues of funding in the industry.

COMPETITIVE LANDSCAPE: COMPARING THE U.S. WITH MALAYSIA AND SINGAPORE

During the semester, the Biotechnology Industry Seminar traveled to Cambridge, Massachusetts, Research Triangle Park, North Carolina, and San Francisco, California, to assess the state of the U.S. biotech industry. It also traveled to Malaysia and Singapore to contrast those nations' approaches to developing a biotechnology sector with the United States.

In general, Malaysia and Singapore differ from the United States primarily in terms of each country's willingness to centralize decision-making and resourcing at the national level. This difference provides both advantages and disadvantages. On the positive side, centralized planning allows a longer-term perspective. Singapore, for instance, budgets for biotechnology (as well as other national priorities) at the national level in five-year increments, giving A*STAR, the organization responsible for planning biotechnology development, stability and the ability to craft long-term strategies. This policy has enabled Singapore to build biotechnology into its second-largest manufacturing sector, has drawn MIT and Duke to build satellite campuses there devoted to scientific research, and has led to the building of a biotechnology cluster similar to those in the United States.[30] Malaysia's central government is also heavily involved in promoting the country as a biotechnology hub through numerous incentives offered to companies.[31]

A major downside to this centralized approach is difficulty fostering the level of innovation that is found in U.S. biotechnology clusters. During our foreign site visits, numerous companies and agencies cited as a challenge the difficulty of sparking innovation – which generally springs from the bottom up – in an environment of top-down governance. Specifically, the more "hands off" approach in the United States allows industry to determine the areas of R&D interest, and seems to be the most productive model. With less innovation, these countries focused on manufacturing and distribution, which are much lower-margin businesses than developing new products. In addition to governance, ethnically based policies, school systems that are geared toward execution vice discovery, and difficulty attracting and retaining top-level personnel (particularly in the case of Malaysia) contributed to a less innovative climate.[32]

Malaysia

In 2005, Malaysia established the National Biotechnology Policy (NBP), which aims to turn the biotechnology sector into a key economic driver, contributing five percent of the nation's GDP by 2020. The NBP was designed to provide a comprehensive roadmap that would foster a conducive ecosystem for accelerated growth in the biotech industry. This has been implemented over three five-year phases.

Malaysia has created an organization to steer R&D in alignment with the priorities set by the Ministry of Biotechnology. The government also provides funding to help Malaysian industry

commercialize basic research. In addition to the previously discussed challenges of a centralized industry business model, it appears Malaysia is further hindered by a weak link between industry and academia in biotech. Government research grants direct to industry also appear to be absent in Malaysia.

Singapore

The government of Singapore has created a significant bioeconomy due to several key traits. It is an easy place to attract local and global talent because of its strong education system, English speaking society, and high living standards. It also fosters a long-term predictable business environment with business friendly policies, including strong intellectual property (IP) protection and a credible judicial system. Singapore also offers "smart" business incentives for biotech companies including tax breaks and credits and government-funded internships and grants. Singapore was also committed to R&D, investing $3.7 billion in biotech between 2011 and 2015.

Singapore's Economic Development Board is extremely aggressive. It has 27 regional offices around the world responsible for recruiting foreign direct investment (FDI) and talent to Singapore. Singapore's government to academia link is A*STAR, its agency for Science, Technology & Research, which is a catalyst, enabler, and convener of significant research initiatives. Singapore committed $8.5 billion in R&D through A*STAR in 2014, funded numerous scholarships, and helped grow over 25,000 jobs since 1990. A*STAR has also created 10 research institutes and 5 industry clusters devoted to biotech.

BIOTECHNOLOGY LINKAGES TO THE NATIONAL SECURITY STRATEGY

In April 2012, the Obama administration published the *National Bioeconomy Blueprint* (NBB). This document labeled the bioeconomy as a presidential priority because of the industry's tremendous economic growth potential and social benefits. IBIS*World* reports that U.S. biotechnology industry value added (IVA), a measure of an industry's contribution to the economy, is expected to outpace U.S. gross domestic product (GDP) growth by more than double through 2021. Biotechnology's strong IVA indicates that it contributes *substantially* to the national economy. This links the U.S. bioeconomy to the 2015 *National Security Strategy* (NSS), which listed "a strong, innovative, and growing U.S. economy" as an enduring national interest. The U.S. economy funds the nation's military capability and underwrites its international influence. The publication of the NBB highlighted biotechnology's importance to strengthening U.S. security interests through the economy but also emphasized biotechnology's societal benefits. Biotechnology innovation will play a major role in mitigating climate change, unlocking green sources to satisfy America's growing energy needs, meeting rising global demand for food, and improving medical care and the quality of life for aging populations.

Exponential population growth, diminishing arable land, lack of food security, pandemic diseases, and the absence of basic human rights fuel the rise in global insecurity, and therefore challenge U.S. national security. The preservation of the basic human right to access food, health, and energy remains a core value of the United States.[33] In the past decade, the biotechnology industry made profound strides in the development of genetically modified plant and animal foods, biofuels, and biopharmaceuticals. U.S. investment and R&D played a significant role in increasing global access to nourishment and sustainable energy, and reduced the spread of infectious diseases such as Ebola, HIV/AIDS, and malaria.[34] As the U.S. government incentivizes development, collaboration, and implementation of these emerging technologies, global standards of living will increase, which will subsequently improve international order through increased regional security. [35]

PART TWO – FEELINGS, FRAMEWORK AND FUNDING

INTRODUCTION

After gaining an understanding of how this industry of industries contributes to U.S. economic health and prosperity and to the national security, our seminar wanted to dive deeper. Realizing that each of the subordinate industries had its own markets, regulations, guiding principles, and other industry-specific dynamics, we asked what major policy issues were common across industries, and whether there were areas for improvement. We identified three broad areas with major policy gaps that appear to cut across most, if not all, of the industries currently working in biotechnology. These gaps, if not properly addressed, will eventually stall the rise of biotechnology or lead to crisis as policy and legislation continue to lag behind scientific advances.

The first area is feelings, the ethical and public perception questions raised by the biotechnology industry. American leaders must promote global security and prosperity while protecting the humanity and dignity of all people.[36] Biotechnology provides distinct opportunities to solve enduring human problems, but its responsible use will require exceptional stewardship and adherence to ethnical principles and law. In an era when technology will no longer be the barrier to Huxley's *Brave New World*, it will be more vital than ever to remember that "what we *should* do is more important that what we *can* do."[37]

The second area is the regulatory framework that provides structure and oversight to these disparate industries. With products ranging from health care to fuel to food, biotechnology products are subject to regulation from multiple federal agencies: the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), the Environmental Protection Agency (EPA), the Department of Energy, and various state and local agencies – and that is just in the United States. Marketing these products in foreign countries requires additional review and regulation from host nations' regulatory agencies. This regulatory framework can at times hinder innovation and the ability of firms to bring promising new technologies to market. It is an area ripe for improvement through thoughtful policy.

The third area is funding. Research and product development in biotechnology are enormously expensive. Researchers and firms have many options to get the necessary funds, but each comes with significant drawbacks. Most importantly, the period in the development of a new biotechnology product between invention and commercialization – called the "valley of death" – most commonly financed through public offering or sale of the company to a larger corporation, is under-resourced. This means that many otherwise viable products remain undeveloped. Effective policy reforms could help close that gap.

FEELINGS

In 1993, the Clinton Administration tried and failed to introduce a hardware-based technological solution – the "Clipper chip" – to allow the government to bypass encryption in personal communications devices. In the following decades, devices grew smaller and more capable while encryption technology grew stronger and encompassed more devices and more communications methods. By 2015, Apple's iPhone was entirely encrypted, potentially hindering law enforcement. In February 2016, terrorists responsible for attacks in San Bernardino, California,

left behind a locked, encrypted iPhone that the FBI could not access. At the FBI's request, a court ordered Apple to assist in removing the device's encryption, an order Apple vowed to fight. Twenty years of government inaction amid changing technologies resulted in crisis, leaving one Federal judge to singlehandedly determine the government's policy on encryption. Biotechnology could soon be facing a similar problem.

Biotechnology: On the cusp of revolution

Biotechnology is on the cusp of a revolution that over the next two decades will make the pace of what happened during the past 20 years with encryption and personal technology seem glacial. The vanguard of this revolution is a technology called CRISPR/Cas-9. This technology, which can cheaply and easily make very precise edits in DNA sequences, altering the functionality of cells (see **Figure 1**), has the potential to cure chronic diseases and to improve our quality of life and safeguard the next generation from all manner of genetic conditions. However, it also has the potential, if used unconstrained, to "alter the nature of the human species."[38]

For the first time, bioethicists are being forced to consider the implications of what have been, until now, largely theoretical concerns – human enhancement, germline modification, the use of animal species' genetic code for their own eradication – in short, Genetically Modified Organisms (GMO's) on a human scale. One doesn't have to look far into history to realize that complacency in this area is dangerous. Indeed, the study of bioethics itself largely stems from a desire to avoid very real – and atrocious – mistakes made in the recent past.

Evolution of Bioethical Principles

The term "bioethics" was invented in 1971,[39] but the impetus behind its foundation stemmed from a series of disturbing events over the preceding 40 years. It has been noted that "the name Tuskegee has become a metaphor for human experimentation abuse,"[40] but other examples abound from that era,[41] reaching their nadir with the Nazi experimentation on human concentration camp subjects during World War II.[42] In the shadow of these horrible transgressions, and as the pace of technology quickened, experts across myriad disciplines started to recognize the need for an ethical framework to guide the use of these technologies.

Their framework began with four principles concerned mostly with the ethics of using human subjects in experiments and trials, with or without their consent. These "fundamental concerns were about respecting human dignity and avoiding using humans as means to an end – as mere instruments or raw material for experimentation."[43] The principles of autonomy, nonmaleficence, beneficence, and justice[44] formed the basis of bioethics, but as the science has advanced from that world to the *Brave New World* of Aldous Huxley, these principles have become less helpful. In May 2016, scientists met to discuss the creation of a synthetic human genome – a person without parents. In this case, the contemporary precedent of parental consent unravels. Who decides if we *should* create artificial life because we *can*? U.S. scientists are currently observing a voluntary moratorium on the editing of human germ line cells using CRISPR or other techniques, but history tells us that science will not sit still for long. In the absence of a clear ethical framework, the decision to – or not to – engage in these activities will end up at the level of individual scientists. Is that what's best?

In its 2010 report *New Directions: The Ethics of Synthetic Biology and Emerging Technologies*, the Presidential Commission on Bioethics identified five foundational ethical principles. In addition to beneficence and justice, the Commission identified "intellectual freedom and responsibility, responsible stewardship, and democratic deliberation" as "relevant to considering the social implications of emerging technologies."[45] These principles are more tailored to research

than to medical care, and are meant to strike a balance that allows innovation and risk in pursuing research at the farthest reaches of the possible while recognizing and potentially mitigating the calamitous implications of dual use technologies or misunderstood second or third order effects.

"Stem cells: where angels fear to tread…"

The Commission's take on how to approach these questions is influenced not just by the headlines of the moment, but also by the nature of the Administration in power. While it has spanned numerous administrations, its chair is a political appointee whose views generally seem to hew to the Administration's. Among other significant differences, the Commission's reports from 2003 and 2004 focused far more on the question of embryonic stem cell research than the 2010 report.

Stem cells are the origin for every type of cell in the human (or any other) animal. There are many types of stem cells, and further understanding them holds the promise of effective therapies for cellular diseases. Over time, however, the use of Human Embryonic Stem Cells (HESCs) has come under intense scrutiny and significant ethical debate because they currently can only be obtained from viable human embryos. HESCs show tremendous promise, but the federally funded research surrounding this type of stem cell is highly scrutinized and regulated by the government – and the moral questions surrounding their use are extensive.

The question of whether using human embryos for research is ethical is part of a broader set of questions surrounding embryonic research. These include not just embryonic stem cell research, but questions of abortion, the ethics of In Vitro Fertilization (do parents at the beginning of an IVF process truly understand the implications of agreeing to disposal, or indefinite storage at great expense, of excess embryos, for instance?), and the equity of providing such expensive services on a fee for service model. These questions have been debated for many years without consensus, and meanwhile, the science marches forward.

The "CRISPR Quandary"

The revolutionary new technology called CRISPR (short for Clustered Regularly Interspaced Short Palindromic Repeats) has changed the game for genetic modification. It was discovered in 2013[46] and scientists immediately recognized its ability to precisely modify the DNA of a cell to change the expression of genes and their resultant proteins. This provides the potential for unprecedented control over biological organisms and their offspring. It "allowed researchers to target and excise any gene they wanted – or even edit out a single base pair within a gene,"[47] and was described in a *New York Times Magazine* article entitled the "CRISPR Quandary" as a genetic "word processor, capable of effortlessly editing a gene down to the level of a single letter"[48] easily and cheaply. Its accuracy has been rapidly improving since its discovery. In April 2016, researchers announced a new method that allows them to "directly convert a single letter of DNA to another… [enabling them to] reverse single-letter mutations that are associated with late-onset Alzheimer's and breast cancer."[49] Although this technology promises a remarkable impact—from cures or substantially improved therapies for diseases like Duchenne muscular dystrophy,[50] many forms of cancer, and other genetic conditions like sickle-cell anemia or beta-thalassemia,[51] to CRISPR-created non-browning mushrooms,[52]—it also raises a significant ethical dilemma.

Potential Crisis: Human Enhancement

Until CRISPR there had been remarkable consistency among bioethicists on the question of human enhancement and manipulation of the human germ line. Nearly every report, and most bioethicists, reached the conclusion stated in the 2003 report *Beyond Therapy: Biotechnology and the*

Pursuit of Happiness: recognizing that there are "considerable risks and uncertainties" tied to these procedures, they side-step the formation of conclusions due to their belief that "this technology is unlikely to be applied to humans any time soon."[53]

The avoidance of serious thinking about the issue of significant and widespread modification of the human germ line, and other animals' germ lines, is a major hole in bioethical theory. Instead of having developed ethical guides or practice, that hole has been filled by a trickle of individual researchers and practitioners grappling with the questions on an ad hoc basis as new discoveries have made such questions less esoteric and more immediate. But in the last two years, the CRISPR/Cas-9 technique for genetic modification has turned that trickle into a flood, and even that is only a sliver of what will be possible over the next 20 years if this technique lives up to even 10 percent of its potential. In that time, the world can expect to see huge advancements in synthetic biology and genetic engineering, genetically modified organisms and foodstuffs, and biofuels. This technique could also be used for human enhancement, allowing experimentation on genes controlling everything from height to weight to musculature to eye color. As one article asked, what would it mean if we could enhance future generations to give "most people an IQ of 140, or a lifespan of 110, even if both figures are well within the normal range?"[54] Is that something we should do? Is it something we can afford not to?

Human enhancement or augmentation is of particular interest to the Department of Defense (DoD), which constantly seeks those technologies that can provide an advantage over potential adversaries. The DoD has pursued human enhancement[55,56] for years, through agencies such as the Defense Advanced Research Projects Agency (DARPA) and the Army Research Lab (ARL). However, relatively little has been written regarding the ethical implications of such technologies. Further, there seems to be a lack of an ethical framework, or mechanisms, in which to consider the myriad issues surrounding human enhancement in an operational military context.

Considering human enhancement from a bioethical perspective, many questions present themselves. Should a soldier have the autonomy to refuse an available enhancement? Is the freedom of choice affected by the operational context or military specialty of the soldier – for instance, an infantryman on regular patrols versus a logistician in the rear area? What are the potential long-term effects (health, social, etc.) on the genetically-modified soldier, especially when s/he returns to civilian life? Would permanent enhancements violate a soldier's basic rights by interfering with their ability to lead a normal life after their period of service?[57] And what of enhancements that have the potential to undermine the soldier's moral responsibility by reducing the soldier's sense of fear or other emotions?[58] Finally, is it ethical *not* to employ enhancements, especially if they can be shown to reduce the risk of death or injury? In the words of one set of authors, "If physiological monitoring and feedback (and regulation, through drugs or other means) can decrease large, immediate, or long-term risks to the life or future well-being of service personnel, it would seem there is a moral obligation to provide those resources and controls."[59]

Genetically Modified Organisms: Perception Is Reality

When public perception enters the fray, these "feeling" questions can become murkier still. On 17 May 2016, the National Academy of the Sciences released a major report announcing that there is "no substantiated evidence that foods from genetically engineered crops were less safe than foods from non-genetically engineered crops."[60] This was the latest salvo in a debate that has come to the forefront of national news since Vermont passed legislation requiring foods derived from genetically engineered crops be labeled.[61] Despite substantial scientific evidence that genetically engineered crops are not unsafe, the public continues to harbor reservations about eating them.[62] The Vermont law is a

harbinger of other uncoordinated State actions, and other nations (particularly in Europe[63]) also have piecemeal regulations on labeling. These different regulations could add significant compliance costs to the manufacturing and distribution of myriad consumer products.[64] Congress should adopt a uniform standard for labeling to avoid costs to food manufacturers associated with adopting products to comply with multiple State-level labeling requirements—costs that will be passed to the consumer.

More broadly, consumer distaste for genetically engineered crops could have significant effects in the long-term. This distaste has sprung from multiple sources, ranging from a lack of outreach from the companies producing genetically engineered crops[65] to large and sophisticated media campaigns by anti-GMO activists.[66] Whatever the source, the views of scientists and the public diverge sharply on the safety of these techniques, yet their use and further research to increase crop yield will only grow in importance as pressures from population growth, global warming, and water supply disruptions increase over the next several decades. In the same period, the meaning of "genetically engineered" will become less clear. As the National Academy of the Sciences report points out, "new techniques, like a way to make small genetic changes in plants using genome-editing, are blurring the distinction between genetic engineering and conventional plant breeding, making the existing regulatory system untenable,"[67] which will undoubtedly muddy the debate between pro- and anti-GMO activists as well.

Currently, the regulatory system for genetically engineered crops is based on the process by which crops are produced – plants produced conventionally via breeding are regulated differently from those produced through genetic engineering. In the seminar's discussions with several firms and scientists involved in crop production, those companies and individuals expressed a clear preference for a product-based regulatory scheme that would focus on the characteristics being designed into the crops, and not the methods by which the characteristics are introduced. This approach is also consistent with the recommendations made by the National Academy of the Sciences.[68] This absence of a regulatory framework consistent with the state of science is not unique to genetically engineered crops and leads to the next major area of policy gaps the seminar addressed.

FRAMEWORK

The United States remains uniquely positioned as the world leader in biotechnology to influence global health and lead the development of sustainable food and energy sources. Responsible growth of biotechnologies requires investment in research and development, commitment to commercialization, protection of intellectual property and development and reform of smart regulatory practices, expansion of educational opportunities, and support for private-public partnerships. Innovation in biotechnology is a critical component of the nation's overall security. Unfortunately, the regulatory mechanisms that provide oversight to the industry have not kept pace with that innovation.

In 1986, several federal organizations working under the Domestic Policy Council Working Group on Biotechnology released the Coordinated Framework for the Regulation of Biotechnology (CFRB). This document described the "comprehensive federal regulatory policy for ensuring the safety of biotechnology research and products" and sought to achieve a balance between adequate regulation ensuring public and environmental safety while maintaining "sufficient regulatory flexibility to avoid impeding" a burgeoning industry.[69] Thirty years ago, the working group sought to answer policy questions by defining a regulatory framework that was adequate for products produced with newly emerging biotechnologies and discoveries. Even the authors of the document realized future scientific development would require refining the framework,[70] but until 2015 no

executive office was charged with reviewing federal regulatory policy despite huge advances in biotechnology capabilities.

This document, and the regulatory apparatus it describes, is seminal to the biotechnology industry's continued prosperity because it defines the interaction between multiple federal regulatory agencies that hold authority over approval of biotechnology products, including the FDA, EPA, and USDA. The financial and economic burden due to regulation on the industry is significant because of the rigorous and lengthy approval process required to bring a biotechnology product to market and also because no single federal agency is responsible for coordinating regulatory requirements within the industry. Despite the CFRB's stated intent and program overview to limit approval authority to a single agency when possible, new biotechnology products often fall under the regulatory jurisdiction of more than one federal agency. The pace of discovery and technological development have outpaced the framework, a self-described "mosaic of existing federal law,"[71] necessitating a long overdue review of government policy.

In October 2015, the U.S. Biotechnology Working Group (BWG), acting under a presidential directive to review the outdated CFRB, issued a request for public review and input. In March 2016, a group headed by the Synthetic Biology Group at MIT released a white paper with considerations for the BWG. Specifically, the white paper notes that new biotechnologies cut across traditional regulatory and statutory authorities and agency responsibilities and requests clarification of agency purview under a new CFRB.[72] The white paper illustrates that the 1986 framework includes definitions and descriptions of science that are not adequately applicable to new technology. The paper also recognizes that the old CFRB focused on "the regulation of the product rather than the process" in pharmaceuticals and that "novel emerging products do not fit well within existing product-based regulations."[73] This academic view of the regulatory process conflicts with the desires of various industrial partners encountered during research visits and interviews by the Biotechnology Industry Seminar. As previously described, these partners claim a product-based regulatory framework would ease the economic burden on industry, contribute to the stability of the approval process, and foster innovation. Although the paper's recommendations on regulatory and statutory authority and technical and administrative updates bear serious merit, a multi-disciplinary panel should be formed to consider a product vs. process based regulatory framework.

In response to a BWG request to consider broader issues associated with regulating biotechnology, the white paper also lists additional recommendations that should be adopted. First, the regulatory decision-making process for biotech should utilize a "planned adaptation" strategy. This means that rather than a "one size fits all" regulatory approach, new product approvals should be able to incorporate previous research, policies, tools and schedules to determine authorizations; these can then be modified using new data as it is uncovered, lessons learned from past exemplary cases, and templates from current effective agreements.[74] Further, the white paper notes that the regulatory agencies critical to the framework (EPA, FDA, USDA) are underfunded, especially as it relates to research to inform decision-making. This seminar has noted in numerous conversations that personnel (both in overall manpower and talent recruitment) and operations would benefit from additional funding.

As government policy and oversight languish and the country debates the merits of genetically modified organisms, industry and academic innovators continue to develop new biotechnologies. Discoveries in genetic editing and genetic trait suppression are areas where the demand for personalized medicine and food production exceed the pace of the ethical and legal debate. For instance, the seminar visited Precision Biosciences in North Carolina. That company

has developed a nuclease-based genome editing platform called ARCUS that uses natural or synthetic enzymes to edit DNA sequences.[75] ARCUS gene editing reagents can delete, insert, or edit DNA to cure disease and increase food production while avoiding the legal definition of "genetic modification." Similarly, Monsanto is looking into using the natural biological process known as Ribonucleic Acid interference (RNAi) to suppress genetic traits in plants that prevent high crop yields. By inhibiting plants' natural genetic disposition against biotic and abiotic stressors, Monsanto is able to improve crops, increase production, and protect the environment, while avoiding the "GMO" label.[76] Demand for medical and agricultural breakthroughs will continue to encourage bio-scientific discovery that outpaces or works around federal regulation and oversight.

Judicial Impact to Biotechnology Intellectual Property

A major reason the United States has led in biotechnology is its capacity for innovation. Factors like the ability to cluster academia, industry, capital and talent in multiple places (like San Francisco or Cambridge), and liberal bankruptcy laws that do not discourage failure, contribute to U.S. excelling in innovation. Another major driver of U.S. competitive advantage in encouraging innovation is intellectual property (IP) protection (see **Figure 2**). "Intellectual property is the invisible infrastructure of innovation … nowhere is that statement more accurate than in the field of biosciences."[77] The rigorous federal regulatory burdens, lengthy approval process (on the order of 5-10 years for most products), and significant upfront capital requirements would significantly diminish the drive for technological development in biotechnology without IP protection that promises the recoupment of investment. The Tufts Center for the Study of Drug Development estimated that new drugs cost, on average, around $2.9 billion to develop and subsequently bring to market and that roughly 88 percent of all experimental product candidates fail during clinical trials.[78] Recent judicial rulings, however, especially at the Supreme Court level, could significantly limit the patent eligibility of biotechnology products and threaten the U.S. biotechnology industry's capability to develop tomorrow's innovative products.

In 1980, the Supreme Court ruled in *Diamond v. Chakrabarty* that genetically modified organisms were patentable, but clarified three exceptions that precluded patenting "phenomena of nature, products of nature, and mental processes."[79] That precedent held for more than 30 years, until *Mayo Collaborative Services, et al v. Prometheus Laboratories, Inc ("Mayo").* In a historic decision, the Court ruled that a biotechnological diagnostic process that correlated drug treatment with metabolites in a patient's blood was patent ineligible because it attempted to patent a law of nature.[80] In the subsequent ruling of the *Association for Molecular Pathology (AMP) v. Myriad Genetics ("Myriad"),* the Court overturned more than 30 years of established biotech practice when it ruled that isolated genetic sequences were also no longer patentable.[81] The Court's new interpretation of patentable material was solidified in the 2014 case of *Alice Corp. PTY. Ltd. v. CLS Bank International ("Alice").* In *Alice*, the Court outlined a two-step analysis to determine patent eligibility.[82] Since 2015, nine district court cases relating to biotechnology have relied on the precedents set in these cases; in only one case has a court protected the patent eligibility of biotechnological IP.

The 2011 Leahy-Smith America Invents Act (AIA) also introduced significant changes to U.S. patent law. It created a path for *inter partes* review (IPR) of patents through the U.S. Patent Trial and Appeal Board (PTAB). "The availability of IPRs as an alternative for challenging the validity of issued patent claims… is proving to be an extremely important development for patent owners in general, and for biotechnology in particular."[83] IPR eliminates many of the safeguards inherent in the federal court system, and the PTAB has claimed its decisions are not judicially reviewable. The Supreme Court has agreed to review recent Federal Court rulings on issues with the

IPR process, including standards used to review patent eligibility and whether PTAB decisions are "final and non-appealable."[84]

The judicial decisions in *Mayo, Myriad,* and *Alice,* and the subsequent U.S. Patent and Trade Office (PTO) guidance affecting IPR and patent eligible subject matter have reduced IP protection and have the potential to stifle innovation and weaken productivity. The immediate implication for biotechnology is that any company "that derives significant value from a strong patent position, whether real or perceived, should re-evaluate their position in light of *Mayo* and implement strategies for regaining or maintaining that position."[85] The long-term danger is that these rulings could "stifle innovation because companies may [change strategies to] choose to imitate rather than innovate, and investors may not want to continue to fund the research and development that is required to bring products to market."[86]

Additionally, the judicial rulings of *Mayo, Myriad* and *Alice* may hamper industry's ability to raise funds for basic biotechnology research as the commercialization potential for emerging products lessens. Congress should consider legislation that would clarify what constitutes a "law of nature" in biotechnology, to the extent that its Constitutional authority allows. The question of funding extends well beyond IP protection, however, and is the third broad area of policy gaps to which we now turn.

FUNDING

The end products of biotechnology are incredibly expensive to produce. A successful biotechnology company generally requires highly controlled lab spaces, specialized and precisely engineered equipment, and extremely well-educated and skilled scientists and technicians just to develop a product. Bringing the product to market then requires massive investment to proceed through testing, including arduous and time-consuming clinical trials (for pharmaceuticals), as well as marketing, patent protection, and logistical requirements. While estimates vary, one major pharmaceutical company estimated that the cost to bring a single drug to market was between $1.5 to $6 billion, and took between seven and ten years,[87] while other estimates suggest that for every drug that enters the market, nineteen others fail.[88]

One of the greatest challenges for companies in these markets is access to funding, which is needed to defray the significant costs associated with hiring the right (trained and educated) personnel, barriers to market entry, intellectual property protection challenges, and most significantly, U.S. Government regulation. Even after reaching the market, many drugs do not make it onto insurance formularies, which generally prevents them from achieving profitability.

This long, costly, and burdensome development pipeline pressures firms to deliver maximum profits quickly from those drugs that do make it to market. It also leads firms to avoid research and development in certain categories of drug which either have too small a market to recoup costs, are unlikely to be insurable, or are endemic to countries without robust insurance systems.

Insurance companies, meanwhile, struggle to balance demand for these products—some of which can cost hundreds of thousands of dollars—with the need to balance their books. For example, advocacy groups have been unable to convince lawmakers to require insurance companies to reimburse for whole genome sequencing under the Affordable Care Act. Although the sequencing itself costs less than $1000, the development of individualized or personalized treatments based on it

is still expensive, and insurance companies are reluctant to pay large lump-sum costs; they instead pay for lower cost conventional treatments, even if they are less effective, take longer, or cause detrimental side effects. However, genomic sequencing, the first step toward truly personalized health care, is the future of medicine. To assure these treatments are widely adopted, both new funding mechanisms and new metrics for effectiveness must be developed that can show the financial benefit of insurance companies paying more for individualized treatment that results in fewer costly complications or secondary procedures down the road – key factors to healing sick people and restoring their ability to be productive in the economy.[89]

Where drugs have come off of patent, the use of generics (called biosimilars for biotechnology drugs, a new class of pharmaceuticals which function similarly to generics for small molecule drugs), as well as putting downward pricing pressure on drug companies, helps insurance firms to remain profitable, but also reduces the funds available to those drug companies for new R&D and product development. Ensuring access to adequate funding as biotechnology continues to advance will be a significant concern for both public and private interests.

Funding Phases

Using the drug development process as a general model, the biotechnology product development process can be broken into three phases: discovery, development, and commercialization.[90] Technology discovery is often the product of basic research, but the conversion of this knowledge into a marketable product requires the completion of expensive pre-clinical and clinical trials to prove the safety and efficacy of the product. These trials, mandated by regulation, constitute the development phase of the process. The biotechnology ecosystem does not provide universally reliable funding to support this "bench-to-bedside" transition of basic science into clinical products, so many promising breakthroughs fail to reach the commercialization phase.[91] Consequently, the development phase is often termed the "valley of death,"[92] and applies to all biotechnology products, not just pharmaceuticals.

Methods of Funding

The U.S. government and private industry provide the majority of funding for biotech research, especially basic research. Once commercialization starts, about 50 percent of small biotech companies' funding comes from senior partners in the venture, 40 percent comes from public markets, and the remaining 10 percent from venture capitalists and private money.[93] For very early stage companies, internal, venture capital or government grant funding is essential. This money aids the firms as they transfer bench work to the market place and diversify their product portfolios.

Internal funding allows a company to maintain full ownership of the company (retaining both control and profit) and avoid the administrative burden (extensive documentation and lengthy approval process) associated with government grants. However, this option is typically only available to large, established corporations.

Family and friends often provide the initial funding required by small startup companies. Although relatively accessible and often provided with few stipulations, this funding source is typically limited and most often cannot provide enough funding to navigate across the "valley of death."

Venture capitalists, angel investors, and "ultra-high asset investors" with specific focus can

provide sufficient funding to carry product development through the "valley of death" but they are often reluctant to invest unless the technology is a clear game-changer and potential financial blockbuster. Funding from venture capitalists also typically comes with significant conditions—most notably, they generally require a large equity stake in the company. These investors, known colloquially as "smart money," also tend to insert themselves into the business and technical decision-making loop as a condition of lending. Venture capital firms typically expect a return on investment within five years, which can conflict with the long development timelines in the industry.

Initial public offerings (IPO) can provide a sizable cash infusion to a company in need of funding. However, the private-to-public conversion will fundamentally alter the governance of the company. The loss of autonomous decision-making associated with going public is a high price to pay for companies committed to preserving the founding vision of the company.

Established biotechnology and pharmaceutical companies can also completely fund a smaller company through an acquisition. As with an IPO, funding through acquisition changes the decision-making dynamic of the acquired company in exchange for funding to complete product development. For some serial entrepreneurs, acquisition by a larger company is the end objective of their business venture.

The U.S. government provides grants and contracts to support private sector research and development, but only a select portion of the money is specifically earmarked for applied research associated with biotechnology product development. DARPA has a Biological Technologies Office that funds some projects with strong future potential at the basic research stage.[94] The NIH has recently created funding vehicles focused on crossing the "valley of death," but these programs amount to only a few percent of the annual NIH budget, with the vast majority of NIH funding directed to basic research.[95] The Biomedical Advanced Research and Development Authority (BARDA) and Joint Project Management Office for Medical Countermeasure Systems (JPM-MCS) both provide funding specifically intended for "valley of death" research, but this funding is restricted to work on biomedical countermeasures for civilian and military use, respectively.

The administrative requirements associated with U.S. government grants complicate the delivery of funds to small companies. In exchange for funding, recipients accept the significant burden of regular program reviews and reporting requirements. These administrative requirements can be particularly cumbersome to small companies with small staffs that are unfamiliar with U.S. government bureaucracy. Risk aversion is also prevalent in the selection process for government grants, particularly NIH funding. It is common for researchers to request funding for work that is essentially finished to ensure successful project completion, a prerequisite of grant approval. Received funding is then applied to a follow-on research project, and the funding request cycle continues.

Federally Funded Research and Development Corporations (FFRDCs) also fit under the umbrella of government funding of research. They perform tasks such as research and development, systems engineering, and technical studies and analyses on behalf of sponsoring federal agencies.[96] Federal agencies provide billions of dollars each year at FFRDCs.[97] During the course of the semester, the seminar visited three such FFRDCs, each engaged in biotechnology R&D.

DoD FFRDC work programs are strictly constrained by Congress each fiscal year. The annual DoD Appropriations Act sets a ceiling on the total amount of staff time that may be put on

FFRDC contracts during that fiscal year. Therefore, each FFRDC must be selective in determining what efforts they will support. Our discussions with the three FFRDCs revealed there is little coordination in conducting or sharing research and development efforts among the sponsoring agencies or among FFRDCs themselves. There should be a structured framework established for these efforts.

Patient advocacy groups and foundations are often the only available sources of funding for the development of drugs that cannot be commercialized profitably (e.g., orphan drugs). These groups are often comprised of family members of a disease victim. These groups may engage in substantial fundraising, but the funding they provide is targeted to niche projects and does not provide widespread support to the broader biotechnology ecosystem.

Finally, there is venture philanthropy, which is most prevalent in the biopharmaceutical sector. Venture philanthropy can be defined as "the investment of capital by a nonprofit disease-focused organization in a for-profit biotechnology or pharmaceutical firm." Notable venture philanthropic organizations include the Bill and Melinda Gates Foundation, the Juvenile Diabetes Research Foundation, the International AIDS Vaccine Initiative, and the Michael J. Fox Foundation for Parkinson's Research. Venture philanthropy can provide the sizable funds required to conquer the "valley of death," but the company is typically required to surrender a portion of autonomous decision-making in exchange for funds.

POLICY RECOMMENDATIONS

- **Recommendation:** Rewrite the National Bioeconomy Blueprint to be directive in nature. It should
    - Provide a national strategy that specifically spells out the federal policies required to develop the future bioeconomy (and identifies the lead agency for each policy)
    - Provide measurable benchmarks
    - Offer states a model (akin to the model criminal code) that they can use to develop biotechnology clusters, using the North Carolina, Massachusetts or California as exemplars.
- **Recommendation**: Direct a White House biotechnology working group with senior level oversight to update the Coordinated Framework for the Regulation of Biotechnology, which should:
    - Propose new legislation which would streamline the federal oversight bureaucracy, currently spread across three agencies (EPA, FDA, and USDA) and multiple legislative requirements.[98]
    - Review the current process-based regulatory scheme in light of changes in technology, and where appropriate (in genetically engineered crops, for instance), evaluate the merits of a product-based system, which would focus on the specific attributes of products vice the process by which those attributes are achieved.
    - Establish a Federal Science Court. This court would exclusively hear complex scientific cases. Design the court along the lines of the European model for the Unified Patent Court (see Figure 1, Appendix A.) which hears all cases relating to patents issued by the European Patent Office, although the U.S. version should hear more than just patent cases, including any complex, scientific cases that involve product liability with wide-ranging impact.
    - Recommend to Congress that it empower an ad hoc committee to examine biotechnology holistically to consolidate Congressional oversight spread across multiple committees.
    - Recommend Congress bring back the Office of Technological Assessment, or perhaps an Office of Biotechnological Assessment, to consider biotech advances with context from experts who understand the implications of the technologies in full.[99]
- **Recommendation**: Bring bioethics to national attention through Presidential remarks on the potential – and potential drawbacks – of CRISPR and similar technologies. Empower the Presidential Commission on Bioethics to form a *standing* ethics panel that forecasts the art of biotechnology 10 years out, and provides ethics guidelines, or scopes the debate, for controversial methods or scientific advances.
- **Recommendation:** Direct the formation of a joint DoD council to review current human enhancement applications and projects, as well as other biotechnologies, with a view toward identifying and illuminating the ethical issues and policy questions underlying them. This council should have representation from the following offices/organizations: USD (AT&L); USD (P&R); ASD (HA); CJCS (including JCIDS process); DHA; and the individual Services – Army, Navy, and Air Force (including Surgeons General).
- **Recommendation:** Pass federal legislation that standardizes nationwide labeling requirements for foods produced with genetically modified organisms to avoid confusion and duplicative standards for agricultural biotechnology.

- **Recommendation:** Reduce delays in H1B visa processing (visas for specialty occupations) and extensions to expedite hiring and retaining foreign workers with specialized skills. Additionally, make it easier for foreign students to remain in the United States longer to complete post-doctoral research and/or work on transformation of research to commercial products, by increasing the extension period for STEM graduates for F1 visas to 36 months from 24.
- **Recommendation:** Increase the amounts of Small Business Innovation Research grants, and reduce the administrative requirements for these grants. Grants intended to spark innovation could have significantly more impact if the government's tolerance for risk and failure were increased in this area.
- **Recommendation:** Clarify patent law on "laws of nature" to protect the innovative biotechnology culture and align U.S. Patent and Trade Office (PTO) and Inter Partes Review (IPR) guidelines more closely to the processes found in the federal court system.
    - The PTO should first utilize the same "most reasonable" claim interpretation instead of a "broadest reasonable interpretation."
    - The PTO should require the same burden of proof as the courts when determining patent validity and should give the same weight to evidence of patentability required by the courts.
    - Policymakers and the PTO must consider a new legal framework for how biotechnology products (especially "biosimilars") will interplay with the IPR framework.
- **Recommendation**: Designate a single FFRDC as the lead for biotechnology and designate a single sponsoring federal agency to coordinate the research, funding, and reporting for biotechnology. The lead FFRDC should act as a federal biotechnology clearinghouse for all Government funding applications, to avoid duplicative overlap of projects.
- **Recommendation:** Study new and creative reimbursement mechanisms that will allow personalized medicine and expensive biopharmaceuticals drug treatments to be accessible to all. This will require developing new metrics using clinical and cost comparitive effectiveness research data to demonstrate value associated with effective long-term health outcomes.

Appendix I: Illustrations

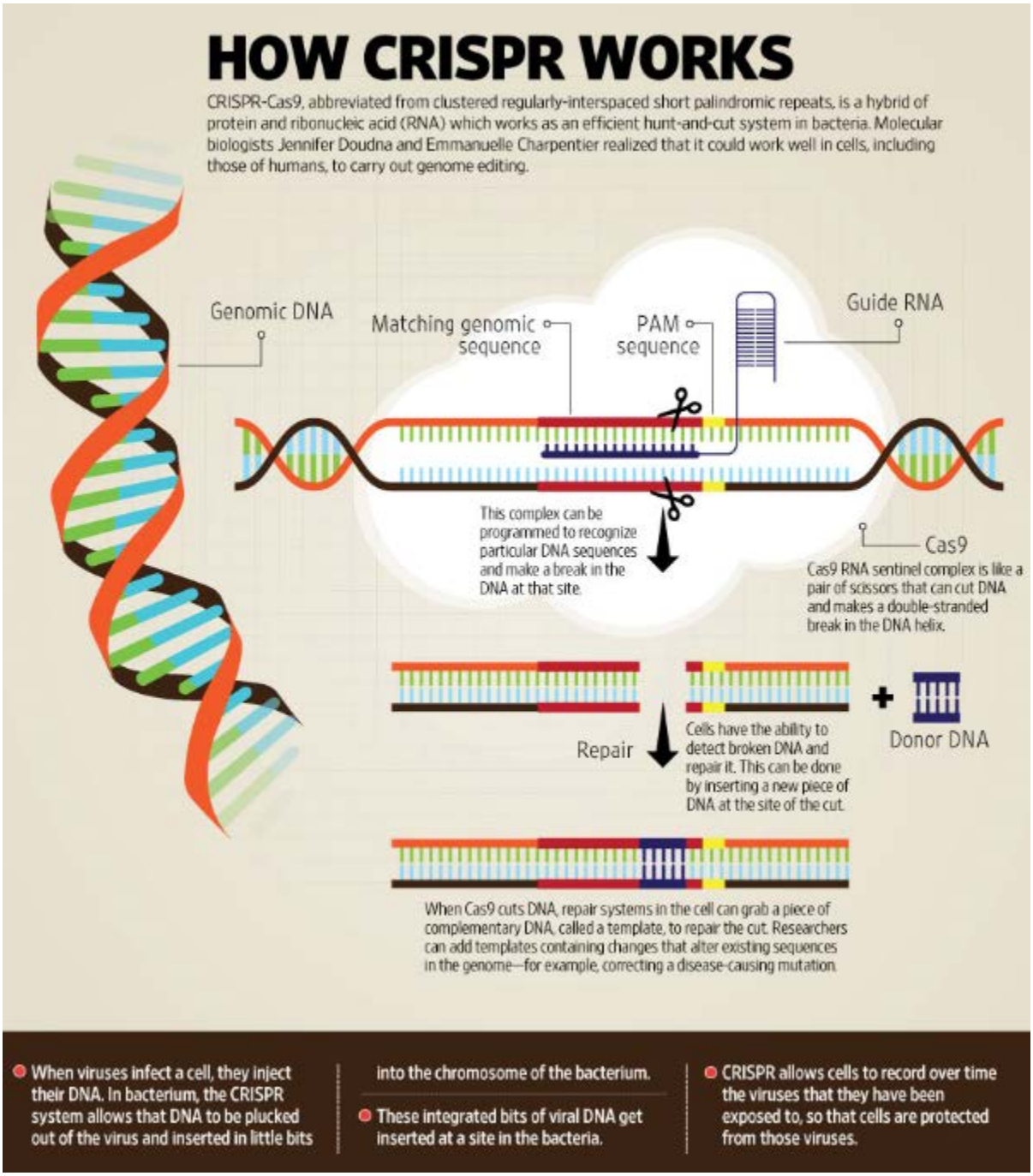

Figure 1. How Genes are Edited using CRISPR-Cas9.[100]

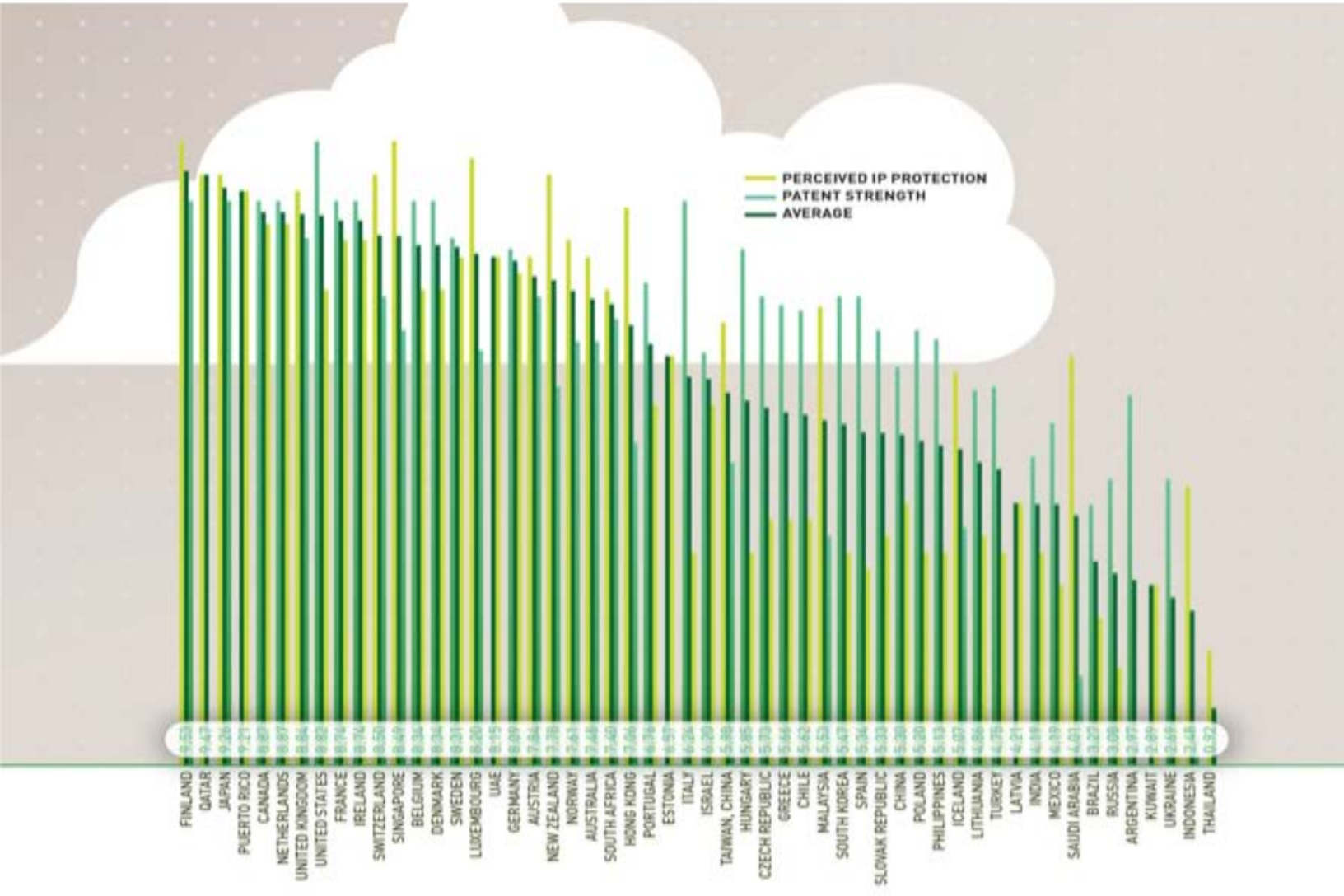

Figure 2. Intellectual Property Protection: Objective and perceived measurements can diverge considerably.[101]

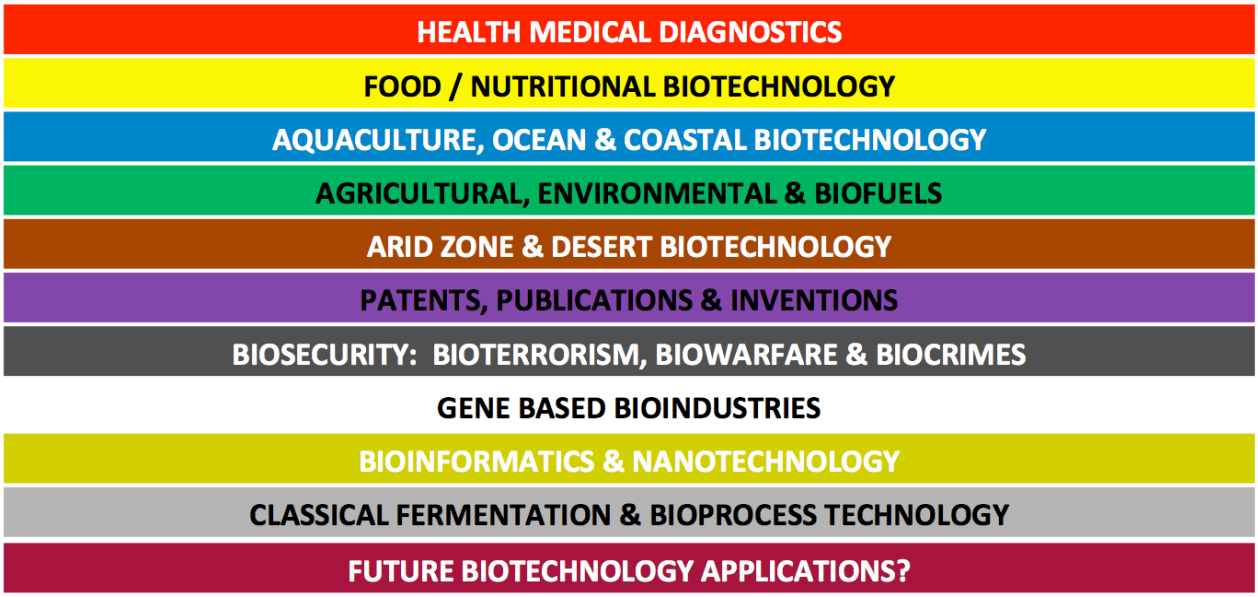

Figure 3. Industries with Applicability to Biotechnology

Notes

[1] Vivek Wadhwa, “How Open Science Can Help Solve Zika and Prepare Us For the Next

Pandemic," The Washington Post, April 20, 2016, accessed April 26, 2016, https://www.washingtonpost.com/news/innovations/wp/2016/04/20/how-open-science-can-help-solve-zika-and-prepare-us-for-the-next-pandemic/.

[2] "Encore une fois: The genomic era arrives, and this time it's probably real," *The Economist*, May 7, 2016, accessed May 10, 2016, http://www.economist.com/news/science-and-technology/21698229-genomic-era-arrives-and-time-its-probably-real-encore-une-fois?frsc=dg%7Ca.

[3] Arthur Caplan, "Using Genetically Modified Mosquitos to Fight Zika is the Right Thing to Do," Forbes, March 16, 2016, accessed 10 May 2016, http://www.forbes.com/sites/arthurcaplan/2016/03/16/using-genetically-modified-mosquitoes-to-fight-zika-is-the-right-thing-to-do/#6a71a21861f4.

[4] Rachel Feltman, "Why this Genetically Modified Mushroom Gets to Skip FDA Oversight," *The Washington Post*, April 18, 2016, accessed May 10, 2016, http://www.forbes.com/sites/arthurcaplan/2016/03/16/using-genetically-modified-mosquitoes-to-fight-zika-is-the-right-thing-to-do/#6a71a21861f4.

[5] Andrew Pollack, "Genetically Engineered Salmon Approved for Consumption," The New York Times, November 19, 2016, accessed May 10, 2016, http://www.nytimes.com/2015/11/20/business/genetically-engineered-salmon-approved-for-consumption.html?_r=0.

[6] Spring 2016 Biotechnology Industry Study visit to Amyris Corporation, April 28, 2016. For more information on the technology, see https://amyris.com/our-company/.

[7] U.S. Congress, Office of Technology Assessment, *Commercial Biotechnology: An International Analysis*, January 1984 (Washington, DC), 3.

[8] Linda Judge, "Biotechnology: Highlights of the Science and Law Shaping the Industry," *Santa Clara High Technology Law Journal* 20, no. 1 (2003): 79, accessed May 18, 2016, http://digitalcommons.law.scu.edu/cgi/viewcontent.cgi?article=1336&context=chtlj

[9] Andrew Pollack, "Scientists Hold Secret Meeting to Consider Creating a Synthetic Human Genome," The New York Times, May 13, 2016, accessed May 15, 2016, http://www.nytimes.com/2016/05/14/science/synthetic-human-genome.html?smprod=nytcore-iphone&smid=nytcore-iphone-share&_r=0.

[10] For a more detailed overview of the industry, see the Spring 2015 Biotechnology Industry Study, "The Bioeconomy and National Security – A True Imperative," Final Report Biotechnology, (Dwight D. Eisenhower School, National Defense University, Washington DC, 2015).

[11] IBISWorld Industry Report, "Biotechnology in the US," www.ibisworld.com, Nov 2015, p. 4. The size of the biotechnology industry compares to $2.5 trillion in revenue and $145.9 billion in

profits for overall agribusiness in the United States, $163.5 billion in revenue and $41 billion in

profit for brand name pharmaceutical manufacturing (plus another $69.5 billion in revenue and $7.7 billion in profits for generic manufacturing) in the United States, and $447.9 billion in revenue and $23.3 billion in profit for petroleum refining in the United States.

[12] Ibid.

[13] U.S. Congress, Office of Technology Assessment, *Commercial Biotechnology: An International Analysis*, January 1984 (Washington, DC), 534. The Seminar noted that this analysis is still one of the best sources of information on the industry, and strongly recommends reestablishment of the Office.

[14] IBISWorld Industry Report, "Biotechnology in the US," www.ibisworld.com, Nov 2015, p. 14

[15] Ibid.

[16] Ibid.

[17] Ibid, p. 19-20.

[18] "The Economic Impact of the US Biopharmaceutical Industry," Battelle Technology Partnership Practice (July 2013): 1, accessed April 21, 2016, http://phrma.org/sites/default/files/pdf/The-Economic-Impact-of-the-US-Biopharmaceutical-Industry.pdf .

[19] Spring 2015 Biotechnology Industry Final Report, 7.

[20] Ibid.

[21] Ibid, 11.

[22] Ibid.

[23] Ibid.

[24] Keith Crane, et al., *Imported Oil and U.S. National Security*, (Santa Monica, CA: RAND Corporation, 2009) 71-74, cited in *Oil Security 2025: U.S. National Security Policy in an Era of Domestic Oil Abundance*, (Washington, DC: Commission on Energy and Geopolitics 2014), 20.
[25] Francesco DeRubertis, Roman Fleck, and Werner Lanthaler, "Six Secrets to success—how to build a sustainable biotech business," Nature, May 27, 2009, accessed April 26, 2016, http://www.nature.com/bioent/2009/090501/full/bioe.2009.

[26] Yali Friedman, *The Business of Biotechnology: Profit from the Expanding Influence of Biotechnology*, (Logos Press, Washington, DC, 2008), 179.

[27] Yali Friedman, "NDU2 Global Biotech 2016" (presentation Dwight D. Eisenhower School, National Defense University, Washington DC, February 4, 2016).

[28] Ibid.

[29] Sean Pool and Elaine Sedenberg, "Hustling for Place-Based Innovation," Science Progress, February 28, 2011, accessed on April 13, 2016, http://scienceprogress.org/2011/02/hustling-for-place-based-innovation/.

[30] Notes and briefing during seminar visit with A*STAR in Singapore, 5 May 2016.

[31] Notes and briefing during seminar visit to the Malaysian Ministry of Science, Technology and Innovation (MOSTI) in Malaysia, 2 May 2016.

[32] Interviews with numerous businesses, agencies, and U.S. Embassies revealed that Malaysian laws favor the ethnic majority Malay population, to include quotas for attending more prestigious universities and government employment. Legally restricting the participation of Chinese and Indian minorities—approximately 25 percent of the population—limits Malaysia's innovation. Similarly in Singapore, ethnic quotas are maintained in all aspects of society, including housing and occupationally.

[33] Barack Obama, "IV. Values," The National Security Strategy, 19.

[34] Barack Obama, "V. International Order," The National Security Strategy, 27.

[35] National Economic Council and Office of Science and Technology, "A Strategy for American Innovation," (October 2015).

[36] Barack Obama, "Executive Summary," The National Security Strategy, (February 2015). https://www.whitehouse.gov/sites/default/files/docs/2015_national_security_strategy.pdf.

[37] National Economic Council and Office of Science and Technology, "A Strategy for American Innovation," (October 2015), 85.

[38] Nicholas Wade, "Scientists Seek Moratorium on Edits to Human Genome That Could Be Inherited," The New York Times, December 3, 2015, accessed April 19, 2016, http://www.nytimes.com/2015/12/04/science /crispr-cas9-human-genome-editing-moratorium.html?_r=0.

[39] Barry Schaller, *Understanding Bioethics and the Law: The Promises and Perils of the Brave New World of Biotechnology*, (Westport CT: Praeger, 2008), 7.

[40] Ibid, 6. The Tuskegee experiment, which began in the 1930s, subjected rural African-American men to syphilis and then left them untreated to study its effects, even after an effective treatment was discovered in the 1940s.

[41] Ibid, see footnotes on Willowbrook, Jewish Hospital, et al.

[42] For an excellent and disturbing eyewitness account, see for example Miklos Nyiszli, *Auschwitz: A Doctor's Eyewitness Account*, (New York: Arcade Publishing, 1960).

[43] Ibid, 6.

[44] Tom Beauchamp and James Childress, *Principles of Biomedical Ethic*s, (New York: Oxford University Press, 1979). The seminal book on biomedical ethics, Beauchamp and Childress's *Principles of Biomedical Ethics*, spells out four ethical principles that are at the heart of biomedical ethics: To summarize these, **autonomy** is concerned with allowing individuals to make their own choices, and is grounded in the writings of Immanuel Kant and John Stuart Mill. Among other things, this principle underlies the requirement for informed consent and disclosure requirements for medical procedures and research subjects. **Nonmaleficence** can best be summarized by the maxim commonly stated in medicine as "above all, do no harm," and concerns such contemporary issues as end-of-life care and assisted suicide, though one could argue its applicability to procedures like genetic testing or genetically modifying crops – often there is a risk-benefit trade off that makes determining what maleficence is tricky. **Beneficence** is the counter point of nonmaleficence, and is defined as "the duty to help others further their important and legitimate interests when we can do so with minimal risk to ourselves." Finally, **justice** in the context of biomedical ethics refers to "distributive justice… the proper distribution of social benefits and burdens," and applies to questions of drug pricing and availability, insurance coverage and other difficult issues. These ethical principles are the bedrock upon which bioethics is built.

[45] Presidential Commission for the Study of Bioethical Issues, "New Directions: The Ethics of Synthetic Biology and Emerging Technologies," (December 2010): 4.

[46] "CRISPR Timeline," The Broad Institute website, accessed April 20, 2016, https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/crispr-timeline.

[47] Jennifer Kahn, "The CRISPR Quandry," The New York Times, November 9, 2015, accessed April 16, 2016, http://www.nytimes.com/2015/11/15/magazine/the-crispr-quandary.html?smprod=nytcore-ipad&smid=nytcore-ipad-share&_r=0.

[48] Ibid.

[49] Arielle Duhaime-Ross, "Breakthrough Method Means CRISPR Just Got a Lot More Relevant to Human Health," The Verge, April 20, 2016, accessed April 23, 2016, http://www.theverge.com/2016/4/20/11450262/crispr-base-editing-single-nucleotides-dna-gene-liu-harvard.

[50] Nicholas Wade, "Gene Editing Offers Hope for Treating Duchenne Muscular Dystrophy, Studies Find," The New York Times, December 31, 2015, accessed April 19, 2016, http://www.nytimes.com/2016/01/01/science/gene-therapy-muscular-dystrophy.html?_r=0.

[51] Heidi Ledford, "CRISPR, The Disruptor," Nature, June 8, 2015, accessed April 15, 2016, http://www.nature.com/news/crispr-the-disruptor-1.17673.

[52] Rachel Feltman, "Why This Genetically Modified Mushroom Gets to Skip USDA Oversight," The Washington Post, April 18, 2016, accessed April 21, 2016, https://www.washingtonpost.com/news/speaking-of-science/wp/2016/04/18/why-this-genetically-modified-mushroom-is-bypassing-usda-regulation/.

[53] Presidential Commission for the Study of Bioethical Issues, "Beyond Therapy: Biotechnology and the Pursuit of Happiness," (October 2003): 47-48.

[54] Guy Kahane and Julian Savulescu. "Normal Human Variation: Refocusing the Enhancement Debate." *Bioethics* 29, no. 2 (2015): 143, accessed April 20, 2016.

[55] Maxwell J. Mehlman, Patrick Lin, and Keith Abney, "Enhanced Warfighters: Risk, Ethics, and Policy," *Case Research Paper Series in Legal Studies*, (January 19, 2013): 17, accessed March 17, 2016, http://ssrn.com/abstract=2202982. Human enhancement is defined as "a medical or biological intervention to the body designed to improve performance, appearance, or capability besides what is necessary to achieve, sustain, or restore health."

[56] Dave Shunk, "Ethics and the Enhanced Soldier of the Near Future," *Military Review* (January-February 2015): 93.

[57] Ibid, 95.

[58] Jessica Wolfendale, "Performance-Enhancing Technologies and Moral Responsibility in the Military," *The American Journal of Bioethics* 8, no. 2 (2008): 28.

[59] Kenneth Ford and Clark Glymour, "The enhanced warfighter," *Bulletin of the Atomic Scientists* 70, no. 1 (2014): 51.

[60] National Academy of Sciences, Engineering, and Medicine Committee on Genetically Engineered Crops, "Genetically Engineered Crops: Experiences and Prospects," Prepublication copy released 17 May 2016, http://www.nap.edu/download.php?record_id=23395, accessed 20 May 2016.

[61] Enactment No. 120 of the 2014 State Assembly of Vermont, accessed 18 May 2016, http://www.leg.state.vt.us/docs/2014/Acts/ACT120.pdf.

[62] See, for example, Roberto A. Ferdman, "Why We're So Scared of GMOs, According to Someone Who Has Studied Them from the Start," *The Washington Post*, July 6, 2015, accessed 18 May 2016, https://www.washingtonpost.com/news/wonk/wp/2015/07/06/why-people-are-so-scared-of-gmos-according-to-someone-who-has-studied-the-fear-since-the-start/.

[63] ICF GHK for DG SANCO, European Commission, "State of Play in the EU on GM-free Food Labeling Schemes and Assessment of the Need for Possible Harmonization," October 2013, accessed 18 May 2016, http://ec.europa.eu/food/plant/docs/gmo-traceability-gm-final_report_en.pdf

[64] Henry I. Miller, "Don't Believe the Anti-GMO Activists: The Costs of a 'Genetically Modified' Label are Huge," Forbes.com, 28 October 2016, accessed 18 May 2016, http://www.forbes.com/sites/henrymiller/2015/10/28/a-genetically-modified-label-costs-way-more-than-you-think/#248c50aa7ae3.

[65] Seminar discussions with several companies including Syngenta and Monsanto indicated that historically, the lack of public engagement from these companies has largely been a result of a mismatch between who their customer is – farmers who have a sophisticated understanding of the science behind these technologies – and who actually impacts the public conversation: end users, grocery store customers who are bombarded by media and concerned about the food they buy for their families. In these conversations, these companies noted that they are aware of this mismatch and have been working to improve their outreach to the end user of their products.

[66] For one example of this high level of media savvy, see Michael Specter, "Seeds of Doubt: An Activist's Controversial Crusade against Genetically Modified Crops," *The New Yorker*, 25 August 2014, accessed 18 May 2016, http://www.newyorker.com/magazine/2014/08/25/seeds-of-doubt, in which the author writes of the activist Vandana Shiva, "Shiva maintains a savvy presence in social media, and her tweets, intense and dramatic, circulate rapidly among tens of thousands of followers across the globe. They also allow her to police the movement and ostracize defectors."

[67] Andrew Pollack, "Genetically Engineered Crops are Safe, Analysis Finds," The New York Times, 17 May 2016, accessed 20 May 2016, http://www.nytimes.com/2016/05/18/business/genetically-engineered-crops-are-safe-analysis-finds.html?smprod=nytcore-ipad&smid=nytcore-ipad-share.

[68] National Academy of Sciences, Engineering, and Medicine Committee on Genetically Engineered Crops, "Genetically Engineered Crops: Experiences and Prospects," Prepublication copy released 17 May 2016, accessed 20 May 2016 http://www.nap.edu/download.php?record_id=23395, p. xviii, which states, "National regulatory processes for GE crops vary greatly because they mirror the broader social, political, legal, and cultural differences among countries. Those differences are likely to continue and to cause trade problems. Emerging genetic technologies have blurred the distinction between genetic engineering and conventional plant breeding to the point where regulatory systems based on process are technically difficult to defend. The committee recommends that new varieties—whether genetically engineered or conventionally bred—be subjected to safety testing if they have novel intended or unintended characteristics with potential hazards. It proposes a tiered approach to regulation that is based in part on new -omics technologies that will be able to compare the molecular profiles of a new variety and a counterpart already in widespread use. In addition, GE crop governance should be transparent and participatory."

[69] U.S. Congress Office of Science and Technology Policy, *Coordinated Framework for Regulation of Biotechnology*, June 1986, 3.

[70] Ibid, 4.

[71] Ibid, 5.

[72] Kenneth Oye, et al., "On Revision of the Coordinated Framework for the Regulation of Biotechnology," *Synthetic Biology Group, Massachusetts Institute of* Technology (March 22, 2016): 2. This white paper lists four recommendations that should be incorporated into a new CFRB and discusses agency responsibility for biotechnology used to attain products and processes through both unconventional and conventional ends.

[73] Ibid, 5.
[74] Ibid, 7-8.

[75] Precision Biosciences, "What is ARCUS?" 2016, accessed May 13, 2016, http://precisionbiosciences.com/our-approach/arcus-genome-editing/.

[76] Monsanto, "RNA Interference in Plants," 2015, accessed May 13, 2016, http://www.monsanto.com/products/pages/rna-interference-in-plants.aspx.

[77] "IP Protection," *Scientific American Worldview*, 2016, accessed March 25, 2016, http://www.saworldview.com/scorecard/ip-protection/.

[78] George Budwell, "Does Valeant Pharmaceuticals' Downward Spiral Signal the End of An Era." The Motley Fool, 2016, accessed March 23, 2016, http://www.fool.com/investing/general/2016/03/20/does-valeant-pharmaceuticals-downward-spiral-signa.aspx#.Vu9JQGgeoCc.mailto.

[79] Jennifer A. Camacho, "Mayo "nays": The Supreme Court says No to Patenting Laws of Nature," *Journal Of Commercial Biotechnology* 18, no. 3 (June 2012): 70, accessed March 20, 2016.

[80] Joanna T. Brougher and David A. Fazzolare, "USPTO guidance on patentable subject matter: Impediment to Biotechnology Innovation?" *Journal Of Commercial Biotechnology* 20, no. 3 (2014): 38, accessed March 20, 2016.

[81] Ibid, 39.

[82] William B. Raich, Alissa K. Lipton, and Jeffrey M. Jacobstein, "Federal Circuit Decision in Ariosa v. Sequenom Offers Further Clarification on the Scope of Patent-Eligible Subject Matter." *Intellectual Property & Technology Law Journal* 27, no. 9 (2015): 20, accessed March 20, 2016. The two-step process: (1) determine whether a claim is directed to a patent ineligible concept such as a product of nature, natural law, or abstract idea, and if so, (2) determine whether the remaining elements of the claim, alone or in combination, are sufficient to transform the claim into a patent-eligible application.

[83] Ibid. "Biotechnology patent owners seem to be surviving this new process slightly better than other industries, according to a study of IPR claims published in 2015. The study found that almost 40% of IPR petitions filed in Tech Center 1600 had been denied, compared to 21% for

all technologies. And in cases in which the Patent Trial and Appeal Board (PTAB) decides to institute an IPR, the study found that 33% of biotech/pharma patents emerge without having a single claim invalidated, compared to about 22% overall." However, there are significant issues with the review if less than one third of patent claims are surviving review.

[84] Christopher Holman, "*Cuozzo v. Lee:* Supreme Court to Decide Its First *Inter Partes* Review Case," *Biotechnology Law Review* 35, no. 1 (February 2016): 6.

[85] Camacho, *Journal Of Commercial Biotechnology*, 74.

[86] Broughner, 43. It's not just USPTO guidelines that might stifle innovation, but also the Judicial precedents behind those guidelines.

[87] Spring 2016 Biotechnology Industry Study visit to Johnson & Johnson, Singapore, May 5, 2016.

[88] "The Drug Development Process – Step 3: Clinical Research," *U.S. Food and Drug Administration*, November 23, 2015, accessed May 12, 2016, http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm.

[89] Laurie McGinley, "Defective 'Breast Cancer' Genes Aren't Just Dangerous for Women. They're Also Linked to Aggressive Cancer in Men," The Washington Post, 15 May 2016, accessed 15 May 2016, https://www.washingtonpost.com/news/to-your-health/wp/2016/05/15/why-more-men-should-be-tested-for-breast-cancer-gene-mutations/?hpid=hp_hp-more-top-stories_brcamen-748pm%3Ahomepage%2Fstory. Research has shown, for instance, that whether or not men carry a specific genetic mutation has implications for their prognosis with late-stage prostate cancer, but until recently emphasis has been placed only on genetic testing of women for this mutation, which also affects breast cancer.

[90] Yali Friedman, *The Business of Biotechnology*, 35.

[91] Declan Butler, "Crossing the Valley of Death," *Nature* 453 (June 10, 2008), 841.
[92] Ibid, 840.

[93] Yali Friedman, *The Business of Biotechnology*, 144.

[94] Seminar Site Visit with DARPA, 3 May 2016.

[95] Butler, "Crossing the Valley of Death," 840-841.

[96] U.S. Government Accountability Office, *Federally Funded Research Centers -Agency Reviews of Employee Compensation and Center Performance*, (Washington DC, August 2014), 4.

[97] Ibid, 1.

[98] John Holdren, et al., "Improving Transparency and Ensuring Continued Safety in Biotechnology," The Whitehouse, July 2, 2015, accessed April 24, 2016, https://www.whitehouse.gov/blog/2015/07/02/improving-transparency-and-ensuring-continued-safety-biotechnology. The Framework was last updated in 1992 and is woefully out of date. The White House has taken an important first step in directing the three agencies to begin updating this document, but the effort requires dedicated leadership at the top to succeed.

[99] Kim Zetter, "Of Course Congress is Clueless About Tech – It Killed Its Tutor," Wired, April 21, 2016, accessed April 24, 2016, http://www.wired.com/2016/04/office-technology-assessment-congress-clueless-tech-killed-tutor/.

[100] Nikita Mehta, "How Genes are Edited using CRISPR-Cas9," Mint, February 16, 2016, accessed May 1, 2016, http://www.livemint.com/Politics/kb7XfbE2hT9Sxg74Wola3J/How-genes-are-edited-using-CRISPRCas9.html.

[101] "IP Protection," Scientific American, 2016, accessed May 1, 2016, http://www.saworldview.com/wv/cache/file/F65C453A-A4E4-4DC5-A5F00812F4627237.jpg