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THE CODE OF LIFE AND DEATH

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Biotechnology is advancing at an astonishing clip, but our safeguards are decades behind. Given new technologies and economies of scale, it is possible for nefarious actors to assemble deadly viruses from scratch using synthetic DNA ordered off the internet.

The Select Agents statute helps to prevent malicious actors from acquiring dangerous pathogens, but the Department of Health and Human Services has interpreted it to not cover synthetic DNA. Recognizing the gap, HHS issued guidance recommending that gene synthesis companies verify their customers to ensure their legitimacy and screen genetic sequences for matches to pathogen sequences.

Unsurprisingly, voluntary guidance has not inspired full adherence. I argue that HHS should require providers to screen the sequences they provide and that it has the statutory authority to do so. This would improve security and level the playing field.

But it would not be enough. Private companies are not in the best position to perform background checks on their customers, and their economic incentives point the other way. I propose a novel license regime, where every buyer and seller of synthetic DNA and gene synthesis equipment would need to undergo a background check before transacting. In a world where biotechnology will only grow cheaper and easier to use, open access is untenable.

Informed by experts at the frontlines of science, industry, and security, this article advances novel regulatory solutions to counter the risks posed by dual-use biotechnology. If the US wishes to protect its people and remain the leader in the field, it must control who can access the code of life and death.

THE CODE OF LIFE AND DEATH

Braden R. Leach[1]

INTRODUCTION

We are living in a new biotechnological age. Better gene sequencing, synthesis, and assembly methods have given us previously unimaginable abilities to manipulate living organisms.[2] Vaccine platforms have accelerated vaccine development, machine learning has revolutionized protein prediction and design, and gene drives may soon eradicate mosquitos that transmit deadly diseases.[3] The emerging bioeconomy promises "innovative solutions in health, climate change, energy, food security, agriculture, supply chain resilience, and national and economic security."[4]

A major part of this advance is the new field of synthetic biology, which aims to make life easier to manipulate "so that biological traits, functions, and products can be programmed like a computer."[5] By applying engineering principles to biology, we can redesign organisms to create biofuels, biomaterials, and cheaper pharmaceuticals.[6] In 2012, the World Economic Forum ranked synthetic biology as the second key technology for the 21st century, right after informatics.[7]

Given new techniques and economies of scale, business is booming. In the past twenty years, the cost of gene synthesis has fallen

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[1] J.D. 2022, University of California, Berkeley, School of Law; Visiting Scholar at the Johns Hopkins Center for Health Security. I would like to thank Dr. Gigi Gronvall, Dr. Michael Montague, Dr. Richard Bruns, and Doni Bloomfield for sharing their insights. All views and mistakes are my own.

[2] Sam Weiss. Evans et al., *Embrace Experimentation in Biosecurity Governance*, 368 SCIENCE 6487, 138 (2020).

[3] Luke Kemp et al., *Bioengineering Horizon Scan 2020*, ELIFE, 2 (2020).

[4] Exec. Order No. 14081, 87 Fed. Reg. 56849 Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy (September 12, 2022).

[5] Gigi Kwik Gronvall, *US Competitiveness in Synthetic Biology*, 13 HEALTH SEC. no. 6, 378, 378 (2015).

[6] *Synthetic Biology*, NAT'L HUM. GENOME RSCH. INST. (Aug. 14, 2019), https://perma.cc/DM8U-6CE7; Ahmad S. Khalil & James J. Collins, *Synthetic Biology: Applications Come of Age*, 11 NATURE REV. GENETICS 367, 367 (2010).

[7] Global Agenda Council on Emerging Technologies, *The Top 10 Emerging Technologies for 2012*, WORLD ECON. FORUM (Feb. 15, 2012) https://www.weforum.org/agenda/2012/02/the-2012-top-10-emerging-technologies/.

from hundreds of dollars per base pair to fractions of cents.[8] Synthetic DNA generated more than $3.6 billion in 2021[9] and is modeled to reach around $10.6 billion by 2030.[10] While the North American region currently has the largest revenue share, the Asia Pacific region is estimated to grow the fastest this decade.[11]

The cheapest way to obtain DNA is to order gene-length sequences from a commercial gene synthesis company.[12] A researcher could also start with short DNA or RNA sequences (called oligonucleotides, or oligos for short) and chemically stitch them together.[13] Improvements in gene synthesizer machines will allow researchers to assemble longer and longer genetic sequences in-house.[14]

New synthetic biology technology and techniques are destroying barriers to entry.[15] Previously, DNA synthesis required university-level implements and expertise, but now "anyone with a laptop computer can access public DNA sequence databases on the Internet, access free DNA design software, and place an order for synthesized DNA for delivery."[16]

But like all technologies, biotechnology can be used for good or for ill. This is known as the dual-use problem.[17]

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[8] Amanda Kobokovich et. al., *Strengthening Security for Gene Synthesis: Recommendations for Governance*, 17 HEALTH SEC. no. 6, 424 (2019) [hereinafter Center for Health Security].

[9] *Synthetic Biology Market by Tools (Oligonucleotides, Enzymes, Synthetic Cells), Technology (Genome Engineering, Bioinformatics), Applications (Tissue Regeneration, Biofuel, Food, Agriculture, Consumer Care, Environmental) – Global Forecast to 2027*, MKTS. & MKTS. https://www.marketsandmarkets.com/Market-Reports/synthetic-biology-market-889.html; *Synthetic Biology Market Size, Share & Trends Analysis Report By Product (Enzymes, Cloning Technologies Kits), By Technology (PCR, NGS), By Application (Non-healthcare, Healthcare), By End-use, And Segment Forecasts, 2022–2030*, GRAND VIEW RSCH., https://www.grandviewresearch.com/industry-analysis/synthetic-biology-market. These figures include both single- and double-stranded DNA.

[10] *Gene Synthesis Market Size to Hit US$ 10.58 Billion by 2030,* BIOSPACE, (May 3, 2022) https://www.biospace.com/article/gene-synthesis-market-size-to-hit-us-10-58-billion-by-2030/?keywords=IO+Biotech. Synthetic DNA made up the lion's share of the broader synthetic biology market in 2020. *Id.*

[11] *Id.*

[12] Nicole H. Kalupa, *Black Biology: Genetic Engineering, the Future of Bioterrorism, and the Need for Greater International and Community Regulation of Synthetic Biology*, 34 WIS. INT'L L.J. 952, 964 (2017).

[13] *Id.*

[14] *Id.*

[15] GEORGE M. CHURCH & ED REGIS, REGENESIS: HOW SYNTHETIC BIOLOGY WILL REINVENT NATURE AND OURSELVES 158 (2012).

[16] Michele S. Garfinkel et. al., *Synthetic Genomics, Options for Governance*, 5 BIOSEC. AND BIOTERRORISM: BIODEF. STRATEGY, PRAC., AND SCI., 359, 360 (2007).

[17] *See, e.g.*, Gregory D. Koblentz, *Biosecurity Reconsidered: Calibrating Biological Threats and Responses*, 34 INT'L SEC. no. 4, 96, 101 (Spring 2010) ("Biology and biotechnology are subject to a powerful dual-use dilemma: the skills, materials, and

I. THE THREAT

Biological weapons are "the poor man's atom bomb."[18] Whereas nuclear weapons require specialized facilities and materials that are difficult and expensive to produce, biological weapons can be made with readily available materials and equipment.[19] Dr. George Church explains that bioweapons are "potentially more dangerous than chemical or nuclear weaponry, since organisms can self-replicate, spread rapidly throughout the world, and mutate and evolve on their own."[20] And given that synthetic biology has made contorting nature simpler and cheaper, the poor man's atom bomb is much more achievable than even a few decades ago.[21]

Although biological attack may ring of science-fiction, it has been attempted and perpetrated throughout recorded history.[22] The Mongol army likely catapulted dead plague victims over the city walls of Caffa in 1346, colonial militias sent blankets from smallpox hospitals to American Indians, a German spy attempted to infect Allied livestock during World War I, Imperial Japan used bioweapons against the Chinese during World War II, and the South African apartheid regime weaponized HIV and Ebola.[23] The United States, the United Kingdom, and the Soviet Union all had major bioweapons programs in the 20th Century, and the Soviet Union's clandestine program was active until the early 1990s, two decades after it had signed a treaty prohibiting them.[24] As we shall see, nation states are not the only ones who have pursued bioweapons.

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technology to conduct civilian activities such as biomedical research and pharmaceutical production can also be used to produce biological weapons.").

[18] Michael P. Scharf, *Clear and Present Danger: Enforcing the International Ban on Biological and Chemical Weapons Through Sanctions, Use of Force, and Criminalization*, 20 MICH. J. INT'L L. 477, 497 (1999).

[19] *See* Matthew S. Halpin, *Biological Warfare: The Weaponization of Naturally-Occurring Biological Diseases*, 16 HOUS. J. HEALTH L. & POL'Y 259, 266 (2016).

[20] CHURCH & REGIS, *supra* note 15, at 230–32.

[21] *Id.* at 477; Rob Reid, *Deterrence – and the Undeterrable*, MEDIUM (Oct. 11, 2018), https://gen.medium.com/how-tech-empowers-dangerous-lone-wolves-50fa0365335 [https://perma.cc/A53W-S6YT].

[22] *See* MICHAEL T. OSTERHOLM & MARK OLSHAKER, DEADLIEST ENEMY: OUR WAR AGAINST KILLER GERMS 128 (2017).

[23] *See id.*; *see also* MALCOLM DANDO, BIOTERROR AND BIOWARFARE 24 (2006) (explaining that from 1939 to 1942, Imperial Japan's Unit 731 perpetrated a series of "large-scale biological weapons attacks in China," weaponizing cholera, paratyphoid A, anthrax, and plague).

[24] Benjamin D. Trump et al., *Building Biosecurity for Synthetic Biology*, 16 MOLECULAR SYS. BIOLOGY 1, 2 (2020).

A. Non-State Actors

Terrorist organizations have also demonstrated a keen interest.[25] Al-Qaeda investigated the possibility of weaponizing anthrax but the technological challenges proved too much.[26] The Aum Shinrikyo cult pursued bioweapons before turning to chemical weapons, deploying sarin gas in the subways of Tokyo and killing thirteen.[27] While there is no evidence that the Islamic State ever sought bioweapons, its apocalyptic ideology, attempted genocide of the Yazidis in Iraq, use of chemical weapons, and weaponization of commercial drones suggest that it would not be morally opposed. Just as of 2010, fifteen terrorist organizations had showcased an interest in acquiring bioweapons.[28]

On the home front in 1995, a scientist with ties to white supremacist groups obtained three vials of the bacteria that causes plague.[29] Shortly after the 9/11 attacks, anthrax letters to Congress and the media caused five deaths, incurred a billion dollars in cleanup costs, disrupted the US Postal Service, and shuttered Senate offices for almost three months.[30] After a five-year manhunt, the FBI concluded that US government scientist Dr. Bruce Ivins was responsible, though he committed suicide before he could be indicted.[31]

Although we may wish we lived in a different world, the one we inhabit includes some sociopathic individuals and apocalyptic terrorist groups who may try to engineer plagues.[32] And bioweapons will only

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[25] Koblentz, *supra* note 17, at 114; *see also* NATIONAL BIODEFENSE STRATEGY AND IMPLEMENTATION PLAN: FOR COUNTERING BIOLOGICAL THREATS, ENHANCING PANDEMIC PREPAREDNESS, AND ACHIEVING GLOBAL HEALTH SECURITY, WHITE HOUSE 6 (Oct. 2022) ("Multiple nations have pursued clandestine biological weapons programs, and a number of terrorist groups have sought to acquire biological weapons. In addition, advances in biotechnology, including synthetic biology, are making it easier to develop and use biological agents as weapons."); *id.* at 8 ("terrorist groups have found value in pursuing biological weapons, and there can be no confidence that will change in the future").

[26] Koblentz, *supra* note 17, at 104.

[27] *Id.*

[28] *Id.* at 114.

[29] NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES, SEQUENCE-BASED CLASSIFICATION OF SELECT AGENTS: A BRIGHTER LINE 19 (2010) [hereinafter *Brighter Line*].

[30] OSTERHOLM & OLSHAKER, *supra* note 22, at 127.

[31] Koblentz, *supra* note 17, at 115. Ivins worked at the U.S. Army Medical Research Institute of Infectious Disease (USAMRIID), the military's "premier biodefense research facility." *Id. See also* CHRISTIAN ENEMARK, BIOSECURITY DILEMMAS: DREADED DISEASES, ETHICAL RESPONSES, AND THE HEALTH OF NATIONS 38–39 (2017) (detailing the 1995 and 2001 incidents).

[32] Koblentz, *supra* note 17, at 98, 115.

become more compelling to non-state actors.[33] Synthetic DNA has already become incredibly cheap and widespread, and new technologies and techniques will only make it easier to manipulate. Further advances will reduce barriers and increase the pool of individuals who can effectuate harm.[34]

B. Nefarious Paths

Malicious actors could take several different approaches to obtain a bioweapon. They could acquire a deadly pathogen from nature, steal it from a lab, or create a pathogen from scratch using synthetic DNA.[35]

The acquisition of pathogens from nature or from a lab used to be the easier paths, but technological developments have altered the calculus.[36] The de novo synthesis of known pathogens, particularly small viruses, is listed as one of the most pressing biodefense risks according to the 2018 National Academies of Sciences report.[37] And pathogens' genetic sequences are freely available on the internet.[38]

Scientists have repeatedly shown that synthesizing at least some viruses is doable. It has been demonstrated in "the construction of poliovirus, the 1918 influenza virus, and most recently, the virus that causes horsepox," a close cousin of smallpox.[39] For instance, in 2018, Canadian researchers reconstituted an extinct horsepox virus for only $100,000 using mail-order DNA.[40]

To be sure, pathogen synthesis is not something that just anyone can accomplish. It is still thought to be very difficult to synthesize long

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[33] *Id.* at 117.
[34] NATIONAL BIODEFENSE STRATEGY, *supra* note 25, at 8.
[35] Diane DiEuliis et al., *Biosecurity Implications for the Synthesis of Horsepox, an Orthopoxvirus*, 15 HEALTH SEC. 6, 630 (2017).
[36] *See also* Diane DiEuliis et al., *Options for Synthetic DNA Order Screening, Revisited,* 2 MSPHERE 4, 1, 1 (2017) ("using DNA synthesis technologies, a nefarious actor would not need direct access to certain pathogens but could chemically synthesize them using sequence information freely available on the Internet. Once synthesized, they could be 'booted up' to become infectious.").
[37] National Academies of Sciences, *Biodefense in the Age of Synthetic Biology* 39–40, 117 (2018) [hereinafter NAS Report].
[38] DiEuliis et al., *supra* note 36, at 1.
[39] *Id.*; *see also* Koblentz, *supra* note 17, at 101 (stating that poliovirus was built from scratch for the first time in 2002).
[40] Kai Kupferschmidt, *How Canadian Researchers Reconstituted an Extinct Pox Virus for $100,000 Using Mail-Order DNA*, SCIENCE (July 6, 2017) https://www.science.org/content/article/how-canadian-researchers-reconstituted-extinct-poxvirus-100000-using-mail-order-dna.

bacterial genomes, which is why small viruses pose the greater risk.[41] However, Dr. Kevin Esvelt at MIT estimates that at least 30,000 individuals worldwide possess the laboratory skills to follow "public step-by-step protocols to obtain any influenza virus with a published genome sequence from commercially available synthetic DNA."[42]

Furthermore, there are some cases where viral synthesis is likely easier than rummaging around in nature or perpetrating a lab heist. For example, the World Health Organization declared smallpox (variola virus) eradicated from nature in 1980 and now it is held tightly at only two locations in the world—the CDC headquarters in Atlanta and the Vector lab in Novosibirsk, Russia.[43] If terrorists wanted smallpox, they would likely try to build it.[44]

Once an aspiring bioterrorist acquired a deadly pathogen, he could engineer it to make it even more harmful. Modifications could increase "infectivity, virulence, pathogenicity, transmissibility, and/or stability;" make them resistant to vaccines, antivirals, or antibiotics; or allow them to avoid detection or diagnosis.[45]

Another tactic would be to hybridize the pathogen with DNA from other organisms to create a "chimera," although this would require more expertise and effort.[46] A third possibility would be to design a completely

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[41] *See, e.g.*, Center for Health Security, *supra* note 8, at 420 ("At this time, concerns about misuse of gene synthesis to make entire pathogens from scratch are almost entirely limited to viruses. Synthesis of whole cellular genomes, bacterial or fungal, is a much more challenging task that has only been accomplished by a few groups.").

[42] Kevin Esvelt, *How a Deliberate Pandemic Could Crush Societies and What to do About It*, BULLETIN OF THE ATOMIC SCIENTISTS (Nov. 15, 2022). His estimation is based on the number of doctoral degrees conferred in the relevant fields. He also notes that as larger viruses are more difficult to assemble, the number of people capable of synthesizing "coronaviruses and paramyxoviruses such as MERS and measles" are likely only in the "single-digit thousands," and "only one or two hundred are likely capable of assembling huge poxviruses such as variola, the causative agent of smallpox." *Id. See also* MICHAEL T. OSTERHOLM & MARK OLSHAKER, DEADLIEST ENEMY: OUR WAR AGAINST KILLER GERMS 129–30 (2017). ("Tools to fundamentally alter how a virus or bacteria kills, or even potentially transmits, that did not exist in 2001 are now in the hands of many thousands of scientists in universities . . . and commercial labs.").

[43] DiEuliis, *supra* note 35, at 630.

[44] *Id.*

[45] Jesse Kirkpatrick et al., *Editing Biosecurity: Needs and Strategies for Governing Genome Editing* 50, GEORGE MASON UNIV, & STANFORD UNIV. (Dec. 2018) [hereinafter GEORGE MASON & STANFORD].

[46] *See, e.g.*, *Brighter Line*, *supra* note 29, at 112–13 ("Non-trivial chimeric constructions (more wholesale rearrangement and 'assembly' of parts from different organisms into a novel whole) are extraordinarily challenging and would almost certainly require large laboratory resources and iterative optimization in an experimental testing program in susceptible hosts . . .").

novel pathogen, though this is likely still extremely difficult.[47] The most pressing concerns are the synthesis of known pathogens (with blueprints available online) and their relatively simple modifications.

C. Weapons of Mass Destruction

Upon the advent of CRISPR—which allows for the editing of genetic code similarly to copying and pasting in a word document—James Clapper, then-Director of the Office of National Intelligence, grabbed national security headlines by referring to this tool as a Weapon of Mass Destruction.[48]

While the anthrax attacks only killed five, there is little reason to hope that the next attack will be so limited. Unfortunately, "gene editing technologies and an expanding convergence between biotechnology and information technology have enabled precision manipulation of biology, which creates opportunities for harm only wished for during Cold War bioweapons programs."[49] According to one analysis, "the versatility, flexibility, and precision offered by new genome editing techniques, such as CRISPR, increases the attack surface, which encompasses the number, accessibility, and severity of vulnerabilities that could be exploited to cause harm."[50] If a misanthropic group had the resources to design, build, test, and iterate, the result could be catastrophic.

Former US Navy Secretary Richard Danzig has thought much about the risk of catastrophic bioterrorism. Writing back in 2003, he made the case that sophisticated plots would not involve one isolated attack, but a campaign of them over time.[51] Dr. Esvelt has imagined that terrorists could attack multiple travel hubs simultaneously using multiple pathogens, causing scarcely imaginable chaos.[52] To make the illustration more vivid, he notes that if a single terrorist were to release a

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[47] *Id.* at 112. We can view these options "in order of increasing technical difficulty, and therefore decreasing likelihood: *modified* pathogens; *chimeric* pathogens; and *designed* pathogens."
[48] Diane DiEuliis, *Key national security questions for the future of synthetic biology*, 43 FLETCHER F. WORLD AFF. 127, 128 (2019).
[49] DiEuliis et al., *supra* note 36, at 1.
[50] Kirkpatrick et al, *supra* note 43, at 2.
[51] DANDO, *supra* note 23, at 125 (citing Richard Danzig, *Catastrophic Bioterrorism – What is to be Done?*, WASHINGTON: CTR. FOR TECH. AND NAT'L SEC. POL'Y (2003)).
[52] Esvelt, *supra* note 42, at 2.

virus equivalent to SARS-CoV-2, he would have killed more people than he would have by detonating a nuclear warhead in a dense city.[53]

Even that is scarcely the worst-case scenario. We live in a globalized world, where disease could travel to every corner of the earth before the infected even show symptoms.[54] If an engineered virus spread as easily as the omicron variant, but had the lethality of smallpox, which killed about 30% of those it infected, "the subsequent loss of essential workers could trigger the collapse of food, water, and power distribution networks—and with them, societies."[55]

While natural pandemics continue to pose a substantial threat, we must realize that the next global event could be manmade.[56]

D. Biosecurity & Risk Regulation

Biosecurity is the project of keeping people safe from both natural and manmade disease.[57] (This term is often confused with "biosafety," which is concerned with preventing lab accidents.[58]) In the last two to three decades, the US government has explicitly come to view pandemic disease as a national security threat.[59]

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[53] *Id.* at 2. Several other scientists have depicted Esvelt as a scaremonger, but "many agree that *some* kind of security for synthetic DNA is warranted." *See* Michael Schulson,
Experts debate the risks of made-to-order DNA, UNDARK (Dec. 21, 2022) https://undark.org/2022/12/21/experts-debate-the-risks-of-made-to-order-dna/.
[54] OSTERHOLM & OLSHAKER, *supra* note 42 at 131. For instance, after SARS "emerged from rural China in February 2003, it spread to five countries within twenty-four hours and another twenty countries on five continents within two months." Koblentz, *supra* note 17, at 103. Dr. Koblentz argues that "four trends . . . have increased the risks posed by biological threats: advances in science and technology, the emergence of new diseases, globalization, and the changing nature of conflict." *Id.* at 98.
[55] Esvelt, *supra* note 42, at 2.
[56] Jaime M. Yassif et al., *Strengthening global systems to prevent and respond to high-consequence biological threats*, NUCLEAR THREAT INITIATIVE 4 (Nov. 2021).
[57] ENEMARK, *supra* note 31, at xvi. Narrower definitions only capture manmade disease. *See* Koblentz, *supra* note 17, at 107.
[58] *See, e.g.*, National Research Council of the National Academies of Sciences, RESPONSIBLE RSCH. WITH BIOLOGICAL SELECT AGENTS AND TOXINS 27 (2009).
[59] *See, e.g.*, David P. Fidler, *Public Health and National Security in the Global Age: Infectious Diseases, Bioterrorism, and Realpolitik*, 35 GEO. WASH. INT'L L. REV. 787, 793 (2003) (describing, for instance, that the CIA's National Intelligence Council "issued a report in January 2000 entitled *The Global Infectious Disease Threat and Its Implications for the United States*, which presented infectious diseases as a national security threat") (internal citation omitted); James G. Hodge Jr. & Kim Weidenaar, *Public Health Emergencies as Threats to National Security*, 9 J. NAT'L SEC. L. & POL'Y 81, 84 (2017) (noting that the federal government has "repeatedly classified public health crises not just as emergencies, but also as threats to national security").

Improving biosecurity will not involve just one silver bullet. Instead, scholars have framed the goal in terms of a "layered defense" or a "web of prevention."[60] Building a hearty, layered defense (or a tensile web, whichever you prefer) is the best we can hope for to prevent catastrophes and respond effectively.[61] This essay is particularly concerned with one especially low-hanging fruit—"people should not be able to easily order the DNA encoding smallpox from the internet."[62]

But when is regulation justified to mitigate risks? Cass Sunstein has argued that "[w]hen risks have catastrophic worst-case scenarios, it makes sense to pay special attention to those risks, even when existing information does not enable regulators to make a reliable judgment about the probability that the worst-case scenarios will occur."[63] Similarly, Richard Posner has admonished that "catastrophic risks—in the sense of low-probability events that if they occur will inflict catastrophic harm—are, despite their low probability, well worth the careful attention of policymakers."[64] Posner includes bioterrorism among these risks.[65]

These suggestions are sensible. Framed oppositely, it would be foolish to regulate only when probabilities are certain or known to be high when the potential magnitude of harm is vast.[66] But regardless of

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[60] *See generally* DANDO, *supra* note 23, at 129–145 (describing different parts of the web of prevention).

[61] *See id.* at 139 (arguing that we cannot "cover all possible contingencies," but each improvement adds difficulty and helps to deter attacks); *id.* at 144 ("the aim is to make it as difficult as possible" to make "hostile use of biological agents.").

[62] Center for Health Security, *supra* note 8, at 425.

[63] Cass R. Sunstein, *The Catastrophic Harm Precautionary Principle*, 6 ISSUES LEGAL SCHOLARSHIP [i], 1–2 (2007); *see also* Cass R. Sunstein, *Irreversible and Catastrophic*, 91 CORNELL L. REV. 841, 841 (2006) ("when catastrophic outcomes are possible, it makes sense to take special precautions against the worst-case scenarios—the Catastrophic Harm Precautionary Principle.").

[64] Richard A. Posner, *Efficient Responses to Catastrophic Risk*, 6 CHI. J. INT'L L. 511, 525 (2006).

[65] *See also id.* at 515–16 ("The probability of bioterrorism or nuclear terrorism, for example, cannot be quantified, but we have some sense of the range of possible losses that such terrorism would inflict (there really is no upper limit short of the extinction of the human race). We can infer from this that even if the probability of such a terrorist attack is small, the expected cost—the product of the probability of the attack and of the consequences if the attack occurs—probably is quite high.").

[66] A quick caveat: I am not suggesting that we slight "normal" public health problems and devote all our attention to catastrophic bioterrorism. They both deserve more careful attention. Interestingly, some tactics would provide a dual benefit. For instance, improving our ability to detect and respond to infectious diseases would help mitigate both natural and manmade diseases.

whether one is a fan of the precautionary principle or not, my proposed solutions do not hinge on it.[67]

E. US Policy

Simply put, "governments are still imposing old rules on a new technology, an insufficient strategy to provide security in the future."[68] This is unsurprising, given the lightning pace of scientific and technological development. Moreover, the problem is complex and multidisciplinary, existing at the intersection of science, technology, law, and economics. Any legal solutions must take all into account.

This issue has received very little attention in the legal literature. Although several efforts have captured the overall problem, there is a dearth of pragmatic solutions.[69] This essay aims to fill that gap.

After analyzing domestic law, I conclude that the *de facto* self-regulation regime for commercial DNA synthesis is deeply inadequate. The Federal Select Agents Program does not address the synthesis of pathogens from scratch, and it will only grow more outdated as biotechnology improves. Any viable solution must focus on preventing

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[67] A proponent of the strong version of the precautionary principle would demand that synthetic biology be blocked until its proponents could show that it was safe, which would be impossible because DNA is dual use. No one is urging this. *See* Jonathan B. Wiener, *Precaution in a Multirisk World*, HUMAN AND ECOLOGICAL RISK ASSESSMENT: THEORY AND PRACTICE 1509, 1521 (2002). Professor Wiener argues that the precautionary principle is too simple in a world of multiple risks and advocates an "optimal precaution" approach that weighs tradeoffs, considers the risks created by regulation, and tries to minimize overall risk. *See id.* at 1511, 1520. *See also* Jonathan B. Wiener, *The Tragedy of the Uncommons: On the Politics of Apocalypse*, 7 GLOBAL POLICY 67, 76 (May 2016) (finding "the conventional view that the public demands more risk protection while experts urge less turns out to apply to unusual but experienced (available) risks, whereas for both familiar routine risks, and ultra-low-frequency (unexperienced) catastrophic risks, it is not the public demanding more protection, but experts.").

[68] Benjamin D. Trump et al., *Building Biosecurity for Synthetic Biology*, 16 MOLECULAR SYSTEMS BIOLOGY (2020); *see also* Megan J. Palmer et al., *A More Systematic Approach to Biological Risk*, 350 SCIENCE 6267, 1471 (Dec. 2015) (our strategies for "managing biological risk in emerging technologies have not matured much in the last 40 years."); OSTERHOLM & OLSHAKER, *supra* note 42, at 129 ("In spite of biological warfare's long history and our experience of it in my lifetime, in the more than a decade and a half since the 2001 anthrax attack, our state of unreadiness and denial has remained more or less the same.").

[69] *See, e.g.*, Stephen M. Maurer, *End of the Beginning or Beginning of the End - Synthetic Biology's Stalled Security Agenda and the Prospects for Restarting It*, 45 VAL. U. L. REV. 1387 (2011); Braden Leach, *Necessary Measures: Synthetic Biology & the Biological Weapons Convention*, 25. STAN. TECH. L. REV. 141 (2021); Kalupa, supra note 12 at 964.

malicious individuals and entities from easily acquiring gene synthesis materials, including synthetic DNA and related equipment.[70]

I make two major policy prescriptions. First, The Department of Health and Human Services (HHS) should require that gene synthesis companies screen customers' DNA orders for matches to dangerous pathogens. I argue that HHS already has the statutory authority to do so. Second, the US should adopt a license system for buyers and sellers of synthetic DNA. In its simplest formulation, everyone transacting in synthetic DNA and gene synthesis equipment should have to undergo a brief background check. This would erect a necessary barrier to mitigate facile access to powerful dual-use materials.

This essay proceeds in eight parts. In Part II, I summarize the state of US law. In Parts III through V, I explain why HHS should require genetic sequence screening, argue that it already has the statutory authority to do so, and analyze specific policy elements. Part VI argues that the US should implement a license regime for the gene synthesis ecosystem. Part VII builds out the regime, and Part VIII addresses plausible concerns. Part IX briefly concludes.

II. CURRENT LAW

The US primarily relies upon the Federal Select Agents Program ("FSAP") to protect the populace from biological harm. This section surveys the legal landscape and points out its obvious weaknesses given technological progress.

A. Background

The Biological Weapons Convention[71] ("BWC") and its implementing legislation[72] form the backdrop of US biosecurity law.[73] The US signed the BWC in 1972, the Senate ratified it in 1974 (giving

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[70] National Biodefense Strategy, *supra* note 25, at 9 ("No longer confined to sophisticated research laboratories, these technologies are being developed and utilized all over the world, and the necessary expertise, materials, and equipment are widely available.").

[71] Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction." Apr. 10, 1972, 26 U.S.T. 583, 1015 U.N.T.S. 163 [hereinafter BWC].

[72] Biological Weapons Anti-Terrorism Act of 1989, Pub. L. No. 101-298, 104 Stat. 201 (codified as amended at 18 U.S.C. §§ 175–178); *see specifically* § 2, Purpose and Intent.

[73] *Brighter Line*, *supra* note 29, at 157–58.

advice and consent required under Article II of the Constitution),[74] and President Ford signed the instruments of ratification in 1975, whereafter it entered into force with respect to the United States.[75] It was the first multilateral disarmament treaty to ban states from developing and using an entire category of weapons of mass destruction.[76]

The Biological Weapons Anti-Terrorism Act of 1989 implemented the BWC into federal law.[77] It also sought to "protect the United States against the threat of biological terrorism"[78] by authorizing criminal sanctions for developing bioweapons, allowing the government to seize bioweapons, and providing a cause of action for the US to seek injunctions against violators.[79] The Patriot Act of 2001 beefed up the criminal code for those attempting to acquire bioweapons.[80]

B. Federal Select Agents Program

In part because a white supremacist got his hands on plague bacteria in 1995, the US passed the Antiterrorism and Effective Death Penalty Act of 1996 (AEDPA).[81] This was the first list-based attempt at regulating harmful biological agents.[82]

Following the double-blow of 9/11 and the anthrax attacks, Congress passed the Bioterrorism Act of 2002.[83] This law built upon

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[74] *See* Biological Weapons Anti-Terrorism Act of 1989 § 2(a).
[75] *Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction: Status of the Treaty,* UN OFF. FOR DISARMAMENT AFFS., https://perma.cc/U5WA-BGGE (archived Nov. 3, 2021). There are currently 183 State Parties and 109 State Signatories.
[76] *See* Matthew S. Halpin, *Biological Warfare: The Weaponization of Naturally Occurring Biological Diseases*, 16 HOUS. J. HEALTH L. & POL'Y 259, 276–77 (2016); BWC, *supra* note 71.
[77] Biological Weapons Anti-Terrorism Act of 1989 § 2.
[78] Biological Weapons Anti-Terrorism Act of 1989 § 2(a)(2).
[79] 18 U.S.C. §§ 175–177.
[80] Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001, Pub. L. 107–56, 115 Stat. 272. The Patriot Act expanded some criminal code provisions built by the Biological Weapons Act. *See Brighter Line*, *supra* note 29, at 158.
[81] Pub. L. 104–132, 110 Stat. 1214 (1996). Scholars have noted that the government has often responded in a "reactive manner to counter that particular event," rather than look at what is most likely to happen in the future. *See* Diane DiEuliis et al., *Biodefense Policy Analysis—A Systems-Based Approach*, 17 HEALTH SEC. No. 2, 83, 84–85 (2019) [hereinafter *Biodefense Policy*].
[82] *Brighter Line*, *supra* note 29, at 158. Congress tasked the HHS Secretary with issuing regulations governing "the transport of biological agents with the potential to pose a severe threat to public health and safety through their use in bioterrorism." *Id.*
[83] *See* Public Health Security and Bioterrorism Preparedness and Response Act, known as the Bioterrorism Act of 2002, Pub. L. 107–188, 116 Stat. 594.

AEDPA and created the FSAP we know today.[84] Under this regime, the Centers for Disease Control (with authority delegated from HHS) and Department of Agriculture regulate the possession, use, and transfer of "select agents."[85] This is a list of bacteria, viruses, and fungi that have been determined to pose a severe threat to public health.[86]

However, neither agency has regulated synthetic biology materials.[87] (I will use the term "synthetic biology materials" to encompass synthetic DNA and RNA and the equipment used to make them). They seem to believe that their statutory authority does not extend that far.[88]

Since viruses can be made from scratch, the FSAP no longer provides a "compelling management plan."[89] According to a National Academy of Sciences report, "overreliance on the Select Agent list is a systemic weakness affecting many aspects of the United States' current biodefense mitigation capability."[90]

C. 2010 HHS Guidance

Concerned about the "potential misuse of [gene synthesis] products to bypass existing regulatory controls," HHS issued voluntary

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[84] *See* 42 C.F.R. § 73.2 (2005) (Purpose & Scope) ("This part implements the provisions of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 setting forth the requirements for possession, use, and transfer of select agents and toxins.").

[85] This regulatory patchwork is shared between the HHS/CDC and USDA/APHIS. AEDPA tasked the HHS Secretary with issuing regulations governing "the transport of biological agents with the potential to pose a severe threat to public health and safety through their use in bioterrorism," which HHS delegated to the CDC. Pub. L. 104–132, 110 Stat. 1214. The Bioterrorism Act of 2002 then gave the U.S. Department of Agriculture, through its Animal and Plant Health Inspection Service ("APHIS"), the authority to regulate the possession, use, and transfer of biological agents that relate to plant and animal health and products, complementing the authority granted to CDC for human pathogens. Pub. L. 107–188, 116 Stat. 594. The "select agent" regulations are codified in 42 C.F.R. § 73 (2021), 9 C.F.R. § 121 (2021), and 7 C.F.R. § 331 (2021).

[86] *See Brighter Line*, *supra* note 29, at 159.

[87] *See* 7 C.F.R. § 331 (2021); 9 C.F.R. § 121 (2021); 42 C.F.R. § 73 (2021).

[88] *See, e.g.*, CDC, *Applicability of the Select Agent Regulations to Issues of Synthetic Genomics*, https://osp.od.nih.gov/wpcontent/uploads/Applicability_of_the_Select_Agents_Regulations_to_Issues_of_Synthetic_Genomics.pdf.

[89] Palmer et. al, *supra* note 68, at 1472. Scholars at the Johns Hopkins Center for Health Security note that since "biosecurity controls in the United States and many other nations are primarily based on pathogen access," "gene synthesis technologies undercut these protections." Center for Health Security, *supra* note 8, at 420.

[90] NAS REPORT, *supra* note 37, at 102 ("[O]verreliance on the Select Agent list is a systemic weakness affecting many aspects of the United States' current biodefense mitigation capability.").

guidelines for commercial gene synthesis providers in 2010.[91] This guidance has two basic recommendations: sequence screening and customer verification.[92]

Sequence screening means using software to analyze whether DNA sequences are close matches to pathogen sequences. The guidance encourages providers to screen double-stranded DNA orders longer than 200 base pairs for suspicious orders. It recommends cross-checking all orders against the FSAP list, and for international orders, against the Commerce Control List (CCL) as well. Suspicious orders are to be reported to the FBI Weapons of Mass Destruction Directorate.[93]

As for customer verification, the guidance encourages providers to ensure that their customers are "legitimate," i.e., real and peaceful. Providers have a preexisting legal obligation not to do business with customers that are on a prohibited person or entity list.[94]

In sum, providers are encouraged to screen sequences, but they are not required to, and so long as customers are not on a list of malefactors, providers can still sell them genes.

D. Self-Regulation

In the absence of actual regulation, the gene synthesis industry has engaged in limited self-regulation. The International Gene Synthesis Consortium ("IGSC") is an industry group that was formed to "design and apply a common protocol to screen both the sequences of synthetic gene orders and the customers who place them."[95] Companies in the IGSC voluntarily screen DNA orders over 200 base pairs and are supposed to alert other members of their industry group when they receive a

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[91] Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA, 75 Fed. Reg. 62820–03 (Oct. 13, 2010) [2010 HHS Guidance].
[92] *Id.*
[93] *Id.*
[94] These include the Department of Treasury Office of Foreign Assets Control (OFAC) list of Specially Designated Nationals and Blocked Persons (SDN List), the Department of State list of individuals engaged in proliferation activities, and the Department of Commerce Denied Persons List (DPL). *Id.*
[95] *About IGSC,* INT'L GENE SYNTHESIS CONSORTIUM, https://genesynthesisconsortium.org/ (last visited Feb. 25, 2023). IGSC members purportedly screen for US Select Agents, US Commerce Control List (CCL) controlled sequences, Australia Group list agents, and European Union (EU) list sequences.

suspicious order.[96] But implementing the IGSC standards are at each company's discretion and there is no compliance mechanism.[97]

IGSC members allegedly constitute 80% of the commercial gene-synthesis market worldwide, though there is reason to be suspicious of this statistic.[98] In 2013, the group had seven members and as of late 2022, it had twenty-three members.[99] Throughout this entire period, the organization has professed that it encompasses "approximately" 80% of the global market, even as companies have sprouted prodigiously in South Korea and China.[100]

While most prominent US companies screen DNA sequences—presumably because they view it to be in their enlightened self-interest—it is unclear how many US customers are getting their gene products from non-screening providers in the US and overseas.[101] Many smaller US companies do not screen their orders.[102]

Customer verification is undoubtedly even worse off. While it is relatively cheap and simple to run sequences through automated screening software, investigating customers is time-consuming, expensive, and places companies at a competitive disadvantage.[103]

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[96] Diane DiEuliis et al., *supra* note 36, at 1 ("Gene synthesis providers affiliated with the International Gene Synthesis Consortium voluntarily screen double-stranded DNA synthesis orders over 200 [base pairs] to check for matches to regulated pathogens and to screen customers . . . oligonucleotides and tracts of DNA less than 200 [base pairs] are not screened."). IGSC precautions exceed the HHS Guidelines.

[97] GEORGE MASON & STANFORD, *supra* note 45, at 14.

[98] *Id.*

[99] SARAH R. CARTER & ROBERT M. FRIEDMAN, DNA SYNTHESIS AND BIOSECURITY: LESSONS LEARNED AND OPTIONS FOR THE FUTURE, J. CRAIG VENTER INSTITUTE 10 (Oct. 2015) (internal citations omitted) [hereinafter VENTER REPORT].

[100] Whereas the 2010 HHS Guidance listed roughly 45 companies with gene synthesis capabilities, more than 320 companies are now relevant to the field according to recent market research. Center for Health Security, *supra* note 8, at 424. While U.S. companies initially dominated, "international players, particularly Chinese companies, are rapidly increasing their share of the market." VENTER REPORT, *supra* note 99, at 15; *see also* Trump, *supra* note 24, at 4 ("Saudi Arabia is funding research to develop microbial cell factories to produce fuels and chemicals, while Singapore is investing considerable resources into life and environmental sciences research. The Chinese Academy of Sciences is establishing an Institute of Synthetic Biology, which is tasked with the dual responsibilities of fostering roadmaps for future development while establishing safety and security norms for researchers at Chinese institutions.").

[101] *See* DiEuliis, *supra* note 36 at 1–2; VENTER REPORT, *supra* note 99, at 17 ("Although most U.S.- and E.U.-based DNA providers (the IGSC members plus others) follow the recommendations of the HHS Guidance, there are many providers that do not. We spoke with at least two companies that rely on the trust developed with their customers and only rarely screen DNA sequences.").

[102] *See* DiEuliis, *supra* note 36, at 2–3.

[103] *Id.* at 2 ("the HHS Guidance and screening dsDNA orders are increasingly facing serious challenges to their relevance and impact. One challenge is its cost to companies: costs for DNA synthesis continue to decrease, while screening remains

Immaculately trained bio-informaticists must review orders that raise red flags and follow up with customers, which may include verifying addresses and affiliations and analyzing past orders.[104] These costs get baked into the final prices that customers pay. Companies that do not investigate customers (or do so poorly) can offer lower prices and quicker turnarounds.

Thus, according to a 2015 report by the J. Craig Venter Institute, US providers likely "perform only the legally required minimal customer screening using government watch lists . . . [and] [o]utside the U.S. and Europe, there may be even fewer companies practicing biosecurity screening procedures."[105]

One analysis painted a rosy picture of the status quo, noting that this "partnership" between government and industry "has been reasonably successful to date because established companies are highly motivated to prevent any biosecurity mishaps that could implicate their firms or their industry."[106] After all, in "conversations with industry representatives, we repeatedly heard their concern that any biosecurity lapse on their part could result in a public outcry, legal liability, and/or government action that would severely restrict not only an individual company but the industry as a whole with national and international significance."[107]

Fear of public opprobrium, liability, and regulation are powerful motivators, but so is profit. Given that bioterrorism is rare, most firms that seek to maximize margins and market share will not devote more than a pittance of their resources to security.

Under the self-regulation regime, maligned actors can simply buy DNA from the providers that do not screen. And unless they are on a list of bad guys, they are probably in the clear.

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relatively constant, making screening costs an increasingly larger percentage of total costs. In particular, some orders are not clearly problematic but require a highly trained person to make a judgment about proceeding; these ambiguous orders make up a majority of sequence screening costs. Companies that screen risk becoming uncompetitive.").

[104] Center for Health Security, *supra* note 8, at 424 ("The primary cost of screening a sequence, regardless of length, is in human analyst time in the event of a positive sequence match to a threat-list sequence.").

[105] VENTER REPORT, *supra* note 99, at 17.

[106] VENTER REPORT, *supra* note 99, at 8.

[107] *Id.*

E. 2022 HHS Proposed Guidance

HHS recently issued unfinalized, revised guidance.[108] The 2022 guidance attempts to patch many holes from the 2010 document, though it remains nonbinding. In the next section, I will argue that this fact alone makes it inescapably flawed, but for now I will limit myself to the proposed upgrades.

Like the original guidance, "a primary goal is to minimize the risk that unauthorized individuals or individuals with malicious intent will use nucleic acid synthesis technologies to obtain organisms for which possession, use, and transfer is regulated by FSAP and CCL."[109] But it has an additional, "parallel" goal: "limit[ing] the potential for individuals with malicious intent to use synthetic oligonucleotides to create novel high-risk pathogens using sequences from unregulated organisms."[110] In other words, HHS has its eyes beyond the *select* agents paradigm and is worrying about entirely new pathogens as well. The 2022 guidance also:

- Extends beyond "Providers" to include "Third-Party Vendors, Institutions, Principal Users, and End Users."
- Expands the guidance beyond double-stranded DNA over 200 bases to "include both DNA and RNA, as well as both single- and double-stranded oligonucleotides."
- Lowers the screening threshold from 200 base pairs to "50 base pairs or longer if ordered in quantities of less than one micromole, or lengths 20 bp or longer if ordered in quantities of one micromole or greater."
- Recommends that providers of benchtop synthesizers screen customers, track transfers, screen sequences over the internet, verify users, and log data.[111]

The HHS Assistant Secretary of Preparedness and Response is clearly apprised of the threat. Later I will evaluate each of these issues in turn.

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[108] Screening Framework Guidance for Providers and Users of Synthetic Oligonucleotides, 87 Fed. Reg. 25495–499 (Published April 29, 2022) [hereinafter 2022 HHS Guidance].
[109] *Id.* at 25496–97.
[110] *Id.* at 25497.
[111] *Id.* at 25497–98.

F. California Legislation

California was the first state in the union to regulate gene synthesis to any degree, and as of late 2022, it remains the only one to have done so.

After a more ambitious bill was vetoed by Governor Newsom in 2021, a narrower one made it past his desk in the 2022 legislative session.[112] The statute provides that the California State University system "shall" develop "systemwide guidance for purchasing" gene synthesis equipment or products from providers, whereas the University of California system is merely requested to do so.[113] This provision, situated peculiarly in California's Education Code, is weak medicine. Whether other states will follow California's lead or take larger steps is anyone's guess.

III. SEQUENCE SCREENING REQUIREMENT

This section will briefly lay out why a sequence screening mandate is necessary. Later I will show that requiring companies to investigate their customers would be unwise because companies would be incentivized to perform the cheapest compliance possible, resulting in pointless security theater.

We now live in an age where synthetic DNA is widely available, viruses can be built from scratch, and pathogens can be modified with synthetic DNA. Bioweapon development is criminalized in the US, but as Professor Christian Enemark notes, "the length of time it took the FBI to complete its investigation [into the anthrax attacks] is a factor weighing strongly against the deterrent value of arrest and punishment."[114] Our regulatory apparatus must adapt.

An obvious place to start is to implement a sequence screening requirement for commercial gene synthesis providers. Companies should be required to run customer DNA orders through a database of Select Agent pathogens to make sure they are not unwittingly assisting in

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[112] The vetoed bill would have required all gene synthesis providers and gene synthesis equipment manufacturers operating in California to be a member of the IGSC or have their screening protocols verified by the State Department of Public Health. It would have also required all recipients of state funding to purchase only from IGSC members or verified manufacturers. A.B. 70, 2021–2022 Assemb., Reg. Sess. (Cal. 2021).

[113] CAL. EDUC. CODE § 66361(a) (West 2022).

[114] ENEMARK, *supra* note 31, at 49; *see also id.* at 38 (explaining that the investigation involved "over ten thousand witness interviews, eighty site searches, review of twenty-six thousand emails, analysis of four million megabytes of computer memory, and the issuing of nearly six thousand grand jury subpoenas.").

bioweapon development. HHS could enforce its rule via audits or investigations and impose liability for noncompliance, which I will discuss in greater depth later.

The fundamental benefit of screening is that it will make acquiring dangerous pathogens more difficult.[115] We should not want nefarious actors to have easy access to "genetic material that could be used to construct pathogenic viruses, including smallpox, Ebola, or influenza."[116] Preventing gene synthesis products from being "easily and directly misused" will also serve as a deterrent.[117] If the costs of pursuing this approach are perceived to be too high, then nefarious actors will steer clear. Additionally, screening may be useful for biosafety efforts "if it prevents imprudent and unsafe ordering of genes from dangerous pathogens without due consideration of risks."[118]

One could argue that the HHS guidance is sufficient because most large US companies follow it. But many smaller companies do not, so individuals can simply buy DNA from the providers that do not screen.[119] A national requirement would remove these weak links.

Companies that already screen may even prefer a mandate because it would level the playing field.[120] Their competitors could not cut costs by neglecting security. And even for newer market entrants, running orders through screening software is unlikely to pose serious burdens, especially if NGOs provide the software for free.[121]

Though screening will make it harder for non-state actors to easily assemble malicious viruses, it will not erase the possibility of biological attacks.[122] State-sponsored actors are "unlikely to be detected or deterred by gene synthesis screening controls, given that they would presumably

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[115] Center for Health Security, *supra* note 8, at 427.
[116] Gigi K. Gronvall, *Needed: Stricter Screening of Gene Synthesis Orders, Customers*, STAT+ (Oct. 5, 2022), https://www.statnews.com/2022/10/05/gene-synthesis-suppliers-tighter-screening-orders-customers/.
[117] Center for Health Security, *supra* note 8, at 427.
[118] *Id.* at 426.
[119] *See* DiEuliis et al., *supra* note 36, at 1; VENTER REPORT, *supra* note 99, at 17.
[120] This is much more desirable than a patchwork of state laws. The only state law on the books is California's, which is a partial solution at best. The California approach only requires that California State University researchers buy synthetic DNA from companies that are members of the IGSC. CAL. EDUC. CODE § 66361(a) (West 2022). Recall that industry group members theoretically do a minimum level of sequence screening and customer verification. But there is no compliance mechanism, economic incentives disfavor customer verification, and whatever verification is performed by less capable private companies. Regulating via an industry group is also deeply questionable from a rent-seeking standpoint.
[121] *See* UNDARK, *supra* note 53.
[122] *See* Center for Health Security, *supra* note 8, at 427.

have their own capacities."[123] Non-state actors in other countries may also be able to acquire unscreened DNA, but the US has the largest market and its efforts can help to create norms or rules worldwide. The goal is not complete victory—which is impossible—but meaningful gains that make bioweapon development harder.[124]

IV. HHS HAS STATUTORY AUTHORITY

HHS has the authority to mandate sequence screening under 42 U.S.C. § 262a, titled "Enhanced Control of Dangerous Biological Agents and Toxins."[125] HHS's authority stems straightforwardly from subsection (c) concerning the possession and use of listed agents, and subsection (b) regarding transfers of listed agents.[126] These subsections' broad authority defeat any narrower interpretation.

Under HHS's current reading, this section only accounts for synthetic DNA if it encodes for a *complete* listed pathogen.[127] But HHS has not imposed any barriers to accessing synthetic DNA, so this reading has no teeth. HHS's interpretation is at odds with the broad delegations of authority in subsections (b) and (c).[128]

A. HHS Shall Govern the Possession and Use of Select Agents

Subsection (a) requires that the Secretary "establish and maintain" a list of agents with the "potential to pose a severe threat to public health and safety."[129] This is the authority for the Select Agents list. Subsection (b) requires the Secretary to regulate "transfers of listed agents and toxins."[130] Then, subsection (c) requires the Secretary to regulate their possession and use.[131]

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[123] *Id.* at 425.
[124] *See, e.g.*, *National Biodefense Strategy*, *supra* note 25, at 11 ("Deter, detect, degrade, disrupt, deny, or otherwise prevent nation-state and non-state actors' attempts to pursue, acquire, or use biological weapons, related materials, or their means of delivery.").
[125] 42 U.S.C. § 262a. This section is part of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002.
[126] 42 U.S.C. § 262a (b), (c).
[127] *See* 42 U.S.C. § 262a; 42 C.F.R. §§ 73.2, 73.3. The Select Agent framework has thus far been interpreted to cover the creation, transfer, and possession of *complete* synthetic genomes on the Select Agents list, not just those of "viable" Select Agents. CDC, *supra* note 88.
[128] *See* 42 U.S.C. § 262a; 42 C.F.R. § 73.3.
[129] 42 U.S.C. § 262a(a).
[130] 42 U.S.C. § 262a(b).
[131] 42 U.S.C. § 262a(c).

Subsection (c) provides that the "Secretary shall by regulation provide for the establishment and enforcement of standards and procedures governing the possession and use of listed agents and toxins, *including* the provisions described in paragraphs (1) through (4) of subsection (b), in order to protect the public health and safety."[132]

Requiring gene synthesis companies to screen their orders for matches to select agents is plainly a procedure "governing" the "possession and use" of select agents.[133] To put it bluntly, it governs who can have and use them. The subsection's broad language easily allows for such an application; in the words of Justice Scalia, "Congress knows to speak in plain terms when it wishes to circumscribe, and in capacious terms when it wishes to enlarge, agency discretion."[134] And importantly, Congress's use of the word "including" shows that HHS is not limited to governing possession and use by regulating transfers.[135] It has other means at its disposal.

Indeed, Congress was worried about this very issue in 2002 when it created the Select Agents Program. In the same piece of legislation, Congress amended the criminal code sections regarding biological weapons.[136] It amended the definition of "biological agent" to include "any naturally occurring, bioengineered or *synthesized component* of any such microorganism or infectious substance . . . ."[137] And Congress imported this definition of "biological agent" into section 262a.[138] This definition provides strong evidence that subsection (c) empowers the HHS Secretary to regulate "synthesized component[s]" of select agents to prevent terrorists from possessing or using the complete products.[139]

HHS's own guidance documents also support this reading. For instance, the 2010 Guidance states that:

> [t]he directed synthesis of polynucleotides could enable individuals not authorized to *possess* Select Agents (or, for international orders, those items listed on the CCL) to *obtain* them through transactions with providers of synthetic [double-stranded] DNA. Such synthesis obviates

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[132] *Id.* (emphasis added).
[133] *See id.*
[134] City of Arlington v. FCC, 569 U.S. 290, 296 (2013).
[135] 42 U.S.C. § 262a(c).
[136] 18 U.S.C. § 178(1); *see also* 42 C.F.R. § 73.1.
[137] 18 U.S.C. § 178(1) (emphasis added) (Congress similarly amended the definition of "toxin." in section 2)); *see also* 42 C.F.R. § 73.1.
[138] 42 U.S.C. § 262a(l).
[139] *Id.*; 18 U.S.C. § 178(1).

> the need for *access* to the naturally occurring agents or naturally occurring genetic material from these agents, thereby greatly expanding the potential *availability* of these agents."[140]

Similarly, the 2022 Guidance notes that "[p]urchasing or synthesizing oligonucleotides could enable individuals without a legitimate and peaceful purpose to *possess* genetic sequences that would pose risks if misused.[141]

An opponent might argue that the statute only addresses the possession of *complete* select agents, and screening would merely serve to prevent the dissemination of their components. If a provider sent a customer part of the smallpox genome, the argument would go, then that individual would not possess smallpox. But because one can possess smallpox by ordering its pieces and fitting them together, this narrow interpretation defangs subsection (c) and overlooks that "biological agent[s]" include their "synthesized component[s]."[142] A skeptic might also argue that Section 262a provides an exhaustive list of security measures, leaving no room for a screening requirement.[143] But this interpretation ignores the word "including" in subsection (c).[144] Limiting the possession and use of select agents by regulating transfers is the floor, not the ceiling.

A screening requirement is straightforwardly permissible under 42 U.S.C. § 262a(c). HHS's hands are not tied.[145]

B. HHS Shall Prevent Access to Select Agents

In addition, HHS can require screening under subsection (b). Subsection (b) states that the "Secretary shall by regulation provide for -- (1) the establishment and enforcement of safety procedures for the transfer of listed agents and toxins . . . (2) the establishment and enforcement of safeguard and security measures to *prevent access to*

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[140] 2010 HHS Guidance, *supra* note 91, at 2 (emphasis added).
[141] 2022 HHS Guidance, *supra* note 108, at 25495 (emphasis added).
[142] 42 U.S.C. § 262a(c), (l).
[143] For instance, subsections (d) and (e) require those seeking to work with select agents to register and HHS to maintain a database of registered persons, the select agents they possess, and where transfers are made to. Subsection (f) allows for inspections, (g) creates exemptions, and so on. 42 U.S.C. § 262a(d)–(g).
[144] 42 U.S.C. § 262a(c); *see, e.g.*, Google LLC v. Oracle Am., Inc., 141 S. Ct. 1183, 1197 (2021) (noting a provision's use of "include" and "including" and determining that "the provision's list of factors is not exhaustive").
[145] *See id.*

such agents and toxins for use in domestic or international terrorism or for any other criminal purpose . . . ."[146]

Requiring gene synthesis companies to screen for select agents is a reasonable way to "prevent access to" select agents.[147] It would cause companies not to transfer them, in whole or in part. This is consistent with the broad language of subsection (b)(2), which provides a purpose to be achieved (preventing terrorists and criminals from accessing select agents), instead a specific process to be employed.[148]

So too here, HHS's guidance supports this interpretation. The "primary goal" of the 2010 Guidance was to "minimize the risk that unauthorized individuals or individuals with malicious intent will *obtain* 'toxins and agents of concern' through the use of nucleic acid synthesis technologies."[149] The 2022 Guidance reiterated this, where a "primary goal is to minimize the risk that unauthorized individuals or individuals with malicious intent will use nucleic acid synthesis technologies to *obtain* organisms for which possession, use, and transfer is regulated by FSAP and CCL."[150] The whole point of the guidance is preventing unauthorized or malicious "access" to select agents.[151]

Again, a skeptic might argue that subsection (b) only gives HHS authority to regulate the transfer of *complete* listed agents, not their genetic components, given its subtitle of "Regulation of transfers of listed agents and toxins."[152] However, this interpretation undercuts the operative language in subsection (b)(2), which requires establishing security measures to prevent access to select agents by terrorists and criminals.[153] It also renders the part of the definition of "biological agent" that includes "bioengineered or synthesized component[s]" meaningless.[154]

In conclusion, HHS can mandate sequence screening under 42 U.S.C. § 262a.

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[146] 42 U.S.C. § 262a (b) (emphasis added).
[147] *See id.*
[148] *Id.*
[149] 2010 HHS Guidance, *supra* note 91, at 3 (emphasis added).
[150] 2022 HHS Guidance, *supra* note 108, at 25496-497 (emphasis added).
[151] *Id.*
[152] 42 U.S.C. § 262a (b).
[153] *Id.*
[154] *Id.* § 262a(l)(1) (incorporating the definition from 18 U.S.C. § 178(1)).

V. SEQUENCE SCREENING POLICY

The concept is straightforward: commercial DNA orders should be screened to prevent facile access to pathogen sequences. But the biosecurity literature evinces disagreement about the specifics.

It is undesirable to be too loose on security or too burdensome on industry. A catastrophe could take countless lives, but over-regulation could kill the goose that lays the golden egg. This section will explain the advantages and shortcomings of various approaches and offer tentative conclusions.

A. Synthesizers

Benchtop synthesizers ought to be regulated. As the name implies, these are machines that produce synthetic DNA in-house, obviating the need to order DNA from commercial providers.[155] Oligo synthesizers, which can print short sequences of single-stranded DNA, have been around for decades and are available on eBay.[156] Gene synthesizers, which can print long strands of double-stranded DNA, are relatively new.[157] These powerful, dual-use machines should be a top priority.

The 2022 Guidance states that benchtop equipment should be designed to have internet connectivity to screen sequences, authenticate legitimate users, and log printed sequence data that the manufacturer is to receive.[158] If the user were not authenticated or tried to print pathogen sequences, the device would not print. Others have considered the possibility of kill-switches.[159] Technical solutions should be paired with a license regime, which I will detail below.

B. Line Drawing

One key dilemma is assigning the minimum sequence length for screening. This choice will majorly affect the screening costs for gene synthesis companies. If the bar is set too high, then the risks of evasion

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[155] *See* Center for Health Security, *supra* note 8, at 423.
[156] *Id.; see also* VENTER REPORT, *supra* note 99, at 20 n.20.
[157] Center for Health Security, *supra* note 8, at 423.
[158] HHS 2022 Guidance, *supra* note 108, at 25497–98.
[159] *See* Center for Health Security, *supra* note 8, at 427. Such "built-in biosecurity controls" could take several forms. For example, "if a researcher wished to create a gene synthesis product that matched a virus on the Select Agents list, the researcher would encounter a non-skippable message on their synthesizer with instructions to contact the provider company for a clearance code to proceed.

increase, but if the bar is set too low, it would also capture synthetic DNA customers who are not trying to build genes.[160]

The 2010 HHS guidance only applied to double-stranded DNA over 200 base pairs.[161] This line was likely drawn as a compromise between security and economic feasibility. The 2022 Guidance recommends screening all DNA over 50 bases long, including single-stranded oligos.[162] It lowers the threshold even further—to 20 bases—if customers order a large enough batch.[163]

The impetus for lowering the threshold is that scientific advancements have made it simpler, cheaper, and more reliable to assemble gene-length sequences from these small pieces.[164] This has created a loophole.[165] Instead of ordering a long sequence that would be screened by most US companies, one could chop it up into smaller pieces, evade screening, and then put the pieces together.

However, lowering the threshold to 50 bases may not be economically feasible for providers. It would vastly increase the number of sequences to be screened, it would apply to more providers (and more types of providers), and it would likely generate lots of false positives because shorter sequences are more likely to be shared with nonpathogens.[166] Scientists at the J. Craig Venter Institute have estimated that the "lessons learned by DNA providers from screening [double-stranded] DNA suggest that screening oligos with a similar

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[160] *See* VENTER REPORT, *supra* note 99, at 19–20; Center for Health Security, *supra* note 8, at 421–22. Scientists at the J. Craig Venter Institute offered a potential solution hinging on what the oligos are likely to be used for. Most oligos are used for polymerase chain reaction (PCR) or gene sequencing purposes, not for gene synthesis. These tend to be short—under 30 bases— and orders tend to have only a few oligos. In contrast, oligos used for gene synthesis are generally 60 bases long (but can be as small as 40 bases), and orders tend to be larger. The HHS recommendation for a 50-base threshold apparently hit the middle of the target.

[161] 2010 HHS Guidance, *supra* note 91, at 10.

[162] 2022 HHS Guidance, *supra* note 108, at 25496.

[163] The full requirement is as follows: "*Synthetic oligonucleotides subject to screening:* DNA or RNA, single- or double-stranded, of lengths 50 base pairs (bp) or longer if ordered in quantities of less than one micromole, or lengths 20 bp or longer if ordered in quantities of one micromole or greater." *Id.* (emphasis in original)

[164] *See,* James Diggans & Emily Leproust, *Next Steps for Access to Safe, Secure DNA Synthesis*, 7 FRONTIERS IN BIOENGINEERING AND BIOTECHNOLOGY 86, 3 (Apr. 2019) (noting that "capacity for generating enormous, diverse pools of oligo-length sequences has grown while lower-cost methods for assembling high-quality, gene-length sequences from oligo pools have been developed and matured.") (internal citations omitted). *See also* Center for Health Security, *supra* note 8, at 421-22.

[165] Diggans & Leproust, *supra* note 165, at 3; *see also* Center for Health Security, *supra* note 8, at 427 ("As technologies that rely on oligonucleotide synthesis to assemble larger pieces of DNA become more common, the need for screening lengths of DNA less than 200 nucleotides in length becomes more important.").

[166] Diggans & Leproust, *supra* note 165, at 3; DiEuliis et al., *supra* note 36, at 2.

procedure would be untenable."[167] Other researchers also see oligo screening as cost prohibitive.[168] Overly burdensome asks, in the name of security, could run the gene synthesis industry into the ground.

Although several ideas have been tossed around, they all ignore the most obvious solution—better customer verification.[169]

C. Export and Import Controls

US customers should not be able to circumvent screening by ordering from overseas providers, nor should US companies be able to sell unscreened DNA overseas.

The Commerce Department's Bureau of Industry and Security ("BIS") is responsible for regulating dual-use exports.[170] Under the Export Administration Act, the BIS administers the Export Administration Regulations ("EAR").[171] For our purposes, the EAR implements the Australia Group's Control List, which harmonizes participant states' export controls on pathogens and equipment that could be used to manufacture bioweapons.[172] All Australia Group members, including the US, agree to require entities within their jurisdiction to receive a license before exporting materials on the Control List.[173]

Accordingly, the EAR's Commerce Control List ("CCL") enumerates items subject to licensing requirements, including certain

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[167] VENTER REPORT, *supra* note 99, at 19.
[168] *See* DiEuliis et al., *supra* note 36, at 2.
[169] The Nuclear Threat Initiative endorsed oligo screening but suggested that it be paired with additional resources, tools, and incentives for adherence. *See* Nuclear Threat Initiative, *supra* note 56, at 19-20. James Diggans and Emily Leproust propose screening oligo batches using advanced computational methods that try to predict the puzzle box image that the puzzle pieces will create. *See* Diggans & Leproust, *supra* note 165, at 3. Scholars at the Johns Hopkins Center for Health Security recommend that the government should "fund the development of screening methodologies and standards that could allow for the cost-effective screening of oligonucleotides." Center for Health Security, *supra* note 8, at 427.
[170] *See, e.g.*, Jennifer Feldman, *Trusted Customers in a Distrusted Country: Liberalizing Dual-Use Exports to China While Safeguarding National Security*, 20 FED. CIR. B.J. 337, 343-44 (2010) (describing the dual-use export regime).
[171] *See* Export Administration Act of 1979, Pub. L. No. 96-72, 93 Stat. 503 (expired 1994); 15 C.F.R. §§ 730-774. It has been propped up through executive orders. *See* 15 C.F.R. § 730.
[172] The Australia Group is a multilateral export control regime designed to mitigate the proliferation of biological and chemical weapons. Since 1985, the organization has grown to include 42 participant states plus the European Union. *See Introduction,* AUSTRALIA GROUP, https://www.dfat.gov.au/publications/minisite/theaustraliagroupnet/site/en/introduction.html (last visited Feb. 28, 2023).
[173] *Id.*

pathogens and related equipment.[174] Recent additions include gene synthesizers and genetic sequencing software.[175] Regarding pathogens, the CCL encompasses human, animal, and plant pathogens that are on the Select Agent and Australia Group lists, including synthesized ones.[176] Under the CCL criteria, "genes" that are "specific to" controlled viruses or bacteria are also subject to licensing,[177] but gene *fragments* ostensibly are not.[178]

Critically, the only way to know if controlled genes require an export license is through sequence screening.[179] Gene synthesis companies must run customer orders through screening software to determine whether controlled genes are present. The extent to which US companies comply with this implicit screening requirement for exports is unclear. By contrast, an *explicit* screening rule that applies to domestic and foreign orders alike would be a salutary improvement. The US could also suggest amending the Australia Group Control List to include gene *fragments* that are "specific to" controlled viruses or bacteria, to mitigate

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[174] *See* Commerce Control List, 15 C.F.R. § 774, supp. 1, Category 1.

[175] *See* THE COMMERCE CONTROL LIST, CORPORATE COUNSEL'S GUIDE TO EXPORT CONTROL, App'x Y (2nd ed., last updated Nov. 2022); *see also,* BIS *Considers Export Controls on Neurotechnology and Adds New Controls on Genetic Sequencing Software and Intrusion Software,* DORSEY (Nov. 9, 2021) https://www.dorsey.com/newsresources/publications/client-alerts/2021/11/new-export-controls-on-neurotechnology. ECCN 2B352.j covers "genetic sequencing assemblers and synthesizers that are automated and can generate continuous nucleic acids greater than 1.5 kilobases in length with error rates less than 5% in a single run." Oligo synthesizers are therefore not covered. The newest rule implements an amendment to the Australia Group treaty and covers software designed for gene synthesizers if it is "capable of designing and building functional genetic elements from digital sequence data." ECCN 2D352. These licensing requirements only apply to states subject to restrictions based on chemical and biological weapons and anti-terrorism reasons.

[176] *See* THE COMMERCE CONTROL LIST, CORPORATE COUNSEL'S GUIDE TO EXPORT CONTROL, App'x Y (2nd ed., last updated Nov. 2022). Export Control Classification Number (ECCN) 1C351 contains human and animal pathogens, and ECCN 1C354 lists plant pathogens. The Select Agents lists largely overlap but they are not the same. For instance, yellow fever virus is on the Australia Group list but not the Select Agent list.

[177] *Id.* Genes of regulated human, animal, or plant pathogens require an export license if they meet the criteria in ECCN 1C353. Whereas all genes "specific to" controlled viruses require a license, bacterial genes only require a license if they are unique to controlled species and "could endow or enhance pathogenicity" or "[i]n itself or through its transcribed or translated products represents a significant hazard to human, animal or plant health."

[178] One prominent gene synthesis company rationally interpreted the phrase "gene or genes" to exclude gene fragments. *See* James Diggans, *Synthetic Gene-Length DNA: Evolving Export Control Concerns*, TWIST BIOSCIENCE (July 2019).

[179] *See* Piers Millett & Paul Rutten, *COVID-19, SARS-CoV-2, and Export Controls*, 18 HEALTH SEC. 4, 333 (2020) (explaining that some "gene synthesis companies . . . screen their orders, including against export control lists" which entails translating the "lists of controlled pathogens . . . into a database of controlled sequences").

the uninhibited export of gene fragments that can be "trivially assembled into controlled genes."[180]

On the import side, the US should impose a permit requirement for genetic materials coming from non-Australia Group states.[181] Permits would certify that gene products were sold by a screening provider, and that the provider found no sequences of concern. Unscreened genetic materials would be turned away. This rule could be implemented as a Department of Homeland Security, US Customs and Border Protection regulation.[182]

D. Setting a Floor

The US can require that companies screen for specific pathogens without prescribing a certain database that must be used.[183] The screening floor should encompass regulated pathogens—those on the FSAP and CCL lists—and then companies, universities, and defense professionals can innovate beyond that if they wish.[184]

Some have suggested that all companies should use a central screening database, but this may be unwise.[185] Although it could save companies time and money, it would be prone to evasion.[186]

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[180] James Diggans, *Synthetic Gene-Length DNA: Evolving Export Control Concerns*, TWIST BIOSCIENCE (July 2019). The US might also suggest a method whereby Australia Group members could exchange information regarding their sequence screening practices. This would encourage states to enforce export controls for genetic materials.

[181] *See* 42 C.F.R. § 71.54 (Import Regulations for Infectious Biological Agents, Infectious Substances, and Vectors); U.S. Customs and Border Protection, *Importing Biological Materials into the United States*, (Dec. 21, 2022), https://www.cbp.gov/trade/basic-import-export/importing-biological-materials-united-states.

[182] Synthesized components of microorganisms are already encompassed in the definition of "biological materials" that require inspection. *See* U.S. Customs and Border Protection, *Guidance: Clearance of Biological Materials by U.S. Customs and Border Protection-Procedures and Requirements* (Feb. 13, 2023), https://content.govdelivery.com/bulletins/gd/USDHSCBP-3488069?wgt_ref=USDHSCBP_WIDGET_2.

[183] Center for Health Security, *supra* note 8, at 426.

[184] *See id.* The incentive for innovation is that better screening software can reduce companies' costs. For instance, many pathogens contain "housekeeping" genes, which code for basic biological functions, and can be found in other non-pathogenic organisms. A customer order may trip red flags just because it happens to share a housekeeping gene with a pathogen. Rooting out some of these sequences would reduce ambiguities and employee time sinks.

[185] *See* VENTER REPORT, *supra* note 99, at 186.

[186] *See* Center for Health Security, *supra* note 8, at 426.

Concentrated efforts may be devoted to cracking one lock, and once cracked, every provider would be compromised.[187]

Screening software has developed in tandem with the synthetic DNA market, with Battelle Memorial Institute's "ThreatSEQ" being a notable example.[188] The Intelligence Advanced Research Projects Activity (IARPA) has a sequence screening project as well.[189] The market appears to be providing solid services, though the government may wish to provide its own software for free to upstart companies.

E. New Pathogens

The 2022 (unfinalized) guidance worries that malicious individuals may try to create *novel* pathogens using sequences from "unregulated organisms" "that could contribute to pathogenicity or harm."[190] So, HHS asks that providers develop screening methods to encompass these sequences.[191]

This recommendation should not be transmuted into binding regulation. First and most importantly, requiring this would exceed the scope of HHS' statutory authority.[192] Congress specified a list-based approach, so requiring providers to go beyond the list of specified pathogens into the realm of "unregulated organisms" is out of bounds.[193]

Second, this would be extremely technically difficult, which HHS acknowledges.[194] Predicting traits such as pathogenicity and transmissibility from DNA source code "is a prediction problem of the greatest complexity."[195] According to a special committee tasked with

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[187] *See id.* For instance, Dr. George Church recommended creating a centralized, non-profit DNA clearinghouse set up by a federal agency. Companies that receive suspicious DNA orders would be required to report them to the clearinghouse. Staff would make an immediate preliminary assessment and then search their system for similar or related DNA orders from other vendors. However, this sequence-centric approach would be resource intensive, inefficient, and arguably infeasible as the base pair threshold for screening is lowered.

[188] *Id.* at 424.

[189] *Id.* at 424–25. IARPA's program is known as "Functional Genomic and Computational Assessment of Threats (FunGCAT)," which "aims to improve gene synthesis screening to alert providers to sequences of concern."

[190] 2022 HHS Guidance, *supra* note 108, at 25496–97.

[191] *Id.* at 25497.

[192] *See* 42 U.S.C. § 262a.

[193] 2022 HHS Guidance, *supra* note 108, at 25498. HHS likely recognized that this is beyond its statutory authority by referring to "unregulated" organisms.

[194] *Id.* HHS notes that such a database "may not yet exist," but "encourages the development of such a database . . . provided that measures are taken to prevent such a database from being misused."

[195] *Brighter Line*, *supra* note 29, at 2. Certain genes may serve very different functions in different organisms. And the same gene, in the same organism, can lead to different

examining the Select Agent regulations, these traits "cannot plausibly be predicted with the degree of certainty required for regulatory purposes, either now or in the foreseeable future."[196]

Finally, this could lead to massive information hazards.[197] Knowledge about how pathogens cause harm can be used to fight disease or inflict it.[198] Thus, the same information sets that would allow for advanced screening could be used to design new pathogens. The special committee stated that because "prediction and design go hand in hand," "accurate computational prediction of Select Agent characteristics from genome sequences enables computational design and optimization of bioweapon genome sequences."[199]

VI. BEYOND SELECT AGENTS: A LICENSE REGIME

Almost anyone can buy synthetic DNA online, to be delivered in two business days. I have argued that this is untenable and will only grow more so as biotechnology marches on. The FSAP, though it remains necessary, does not fully account for this problem. And while a sequence screening requirement is necessary, it is not sufficient. Companies' economic incentives disfavor customer investigation. If we take incentives seriously, we realize that many companies are unlikely to do this task well, or at all.

Thus, Congress should pass a law creating a license regime administered by HHS.[200] As with the FSAP, buyers and sellers of

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traits under different environmental conditions. Complex interactions between genes can lead to emergent traits, such that the whole cannot be predicted by merely summing the parts. Predicting the harmful properties of pathogens using only their DNA "will require an extraordinarily detailed understanding of host, pathogen, and environment interactions integrated at the systems, organism, population, and ecosystem levels."

[196] *Id.* at 2.

[197] Nick Bostrom defines an information hazard as "a risk that arises from the dissemination of (true) information that may cause harm or enable some agent to cause harm." Nick Bostrom, *Information Hazards: A Typology of Potential Harms from Knowledge*. REVIEW OF CONTEMPORARY PHILOSOPHY 10, 44–79 (2011).

[198] *See, e.g.*, Gregory Lewis et al., *Information Hazards in Biotechnology*, 39 RISK ANALYSIS 5, 975 (2019) (biological knowledge is "increasingly the object of greatest security concern").

[199] *Brighter Line*, *supra* note 29, at 6. Similarly, NTI bio experts think that "broader distribution of a biorisk database is appropriate when it is limited to established virulence factors from regulated pathogens or listed toxins that are already found in publicly available resources." In other words, we should limit ourselves to information that is already out there. *See* NUCLEAR THREAT INITIATIVE, *supra* note 56.

[200] Although HHS could try to implement a license regime under existing statutory authority, using similar arguments to those I gave above, it would likely be found ultra vires. While sequence screening involves hunting for regulated sequences and only

synthetic biology materials would need to undergo a background check by the FBI to receive a license. Gene synthesis companies would be required to verify each customer's license, and middlemen would be required to verify their customers' licenses as well. This would provide accountability from producer to end-user. Licenses would also be required to buy and sell synthesizers.

This is a necessary and perhaps inevitable first line of defense. Although several scholars have suggested a license regime, this is the first effort to give it a fuller treatment.[201]

As a matter of political feasibility, it is worth mentioning that this solution could receive the net support of industry. Although gene synthesis companies would have to verify licenses, they may prefer the ease and information that licenses would provide. The government would be shouldering part of the security burden, instead of leaving it solely to industry.

As creating and editing life becomes even easier, so does creating bioweapons. The government must control who can access precursor materials. A license system would be the most efficient and comprehensive way to accomplish this.

This section provides four policy arguments favoring a license regime. First, companies' economic incentives direct against customer investigation. Second, the government is better at doing it. Third, customer investigation has a relative advantage to sequence screening. And fourth, this solution would help fill many important gaps. The following section will address the specific elements of a license regime.

A. Economic Incentives Disfavor Customer Investigation

Let us look closely at how (some) gene synthesis companies voluntarily screen and investigate. After a customer submits a DNA order, the provider runs the ordered sequences through a database of

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burdens those trying to purchase those sequences, a license regime would apply to the broader gene synthesis ecosystem. The breadth of such a program would likely exceed the commands in 42 U.S.C. § 262a.

[201] In 2009, Professor Stephen Maurer wrote that "[t]he most obvious way to control synthetic DNA is to license the equipment and reagents that make it." Stephen M. Maurer, *End of the Beginning or Beginning of the End? Synthetic Biology's Stalled Security Agenda and the Prospects for Restarting It*, 45 VAL. U. L. REV. 1387, 1421 (2011) (citing Robert Carlson, *Synthetic Biology 1.0*, FUTUREBRIEF (2005), (discussing licensing of scientists); MICHELE GARFINKEL ET AL., SYNTHETIC GENOMICS: OPTIONS FOR GOVERNANCE, at ii (2007) (describing options for registering synthesis machines and owners and people who purchase reagents); George M. Church, *A Synthetic Bio-Hazard Non-Proliferation Proposal* (Aug. 6, 2004) (discussing licensing scheme for reagents and instruments).

listed pathogens. If there are no "hits," the company ships the order. If there are, the provider follows up with the customer.[202] This means asking questions like: who are you? What is your address? What projects are you working on? The company may try to corroborate answers using databases of registered businesses and web searches. After this follow up, almost all orders are shipped, including ones with pathogen matches.[203] If concerns were not ameliorated, the provider contacts the FBI WMD Directorate.[204]

Although a sequence may have triggered further review, the ultimate decision of whether to ship the product turned on a customer investigation.[205] This is the most important part of the process. But as it stands, companies' profit motives point the other way.

The main reason a voluntary approach is inadequate is that it runs against powerful economic incentives.[206] While the cost of gene synthesis has plummeted dramatically due to technological advances and economies of scale, the cost of customer verification has remained relatively fixed.[207] This is because it requires the time and energy of exquisitely trained and well paid experts.[208] Companies bear high costs,

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[202] *See* Center for Health Security, *supra* note 8, at 424 ("Even with this low rate of flagged orders, the cost to dsDNA providers to screen and follow up on these orders will become increasingly burdensome as the profit per base falls. To make up for the decrease in cost per base, companies will have to accept, and therefore screen, more orders").

[203] *See, e.g.*, DiEuliis, *supra* note 36, at 3 ("it is unknown how many synthesis orders are flagged for further screening, whether customer screening accomplishes much of the same goals as sequence screening, or how many orders are currently referred to authorities. Customer screening is undeniably important . . .").

[204] VENTER REPORT, *supra* note 99, at 8.

[205] This portion of the essay benefitted enormously from conversations with Dr. Michael Montague.

[206] *See, e.g.*, Diggans & Leproust, *supra* note 171, at 4 ("Especially for companies whose business model focuses on thin margins or low volume, the current economics (even with extensive IGSC advice and support) strongly disincentivize screening.").

[207] *See id.* at 2 ("As scale drives down cost per base pair, the relatively fixed cost of screening plays a more direct role in overall price. These costs are driven by both customer and sequence screening—commercially-available customer screening solutions still require a great deal of manual review of false positive findings. These false positives create a floor on the possible reduction in labor cost of new customer onboarding").

[208] *See, e.g.*, Center for Health Security *supra* note 8, at 424 ("Compared to the time required for customer follow-up, the time required for sequence screening is relatively small—on the order of minutes. Red hits can take several hours to resolve during the customer follow-up phase, because the information needed to verify and then complete these orders cannot be gleaned from a database but rather must be gathered from the customer. Thus, the customer screening and follow-up component of biosecurity controls for the dsDNA provider will continue to represent a nontrivial burden on overhead costs of gene synthesis.").

which get translated into higher prices, which in turn make companies less competitive.

The little research available strongly suggests that companies are not willing to sacrifice their competitiveness, which squares with common sense. Several large companies have readily admitted that they only exclude customers if they are found on a list of prohibited persons, and smaller companies are unlikely to do more.[209]

Companies that investigate customers are at a competitive disadvantage.[210] A license system fixes this problem by putting it in the hands of the government. And companies may prefer it that way.

B. The Government Is Better at Background Checks

As I alluded, customer investigation is essentially a background check. This is a quintessential law enforcement task. Since the FBI Criminal Justice Information Services Division already does background checks for those who work with dangerous pathogens under FSAP, it is the obvious candidate to do background checks here as well.[211]

While the FBI is relatively good at performing background checks, gene synthesis companies, resellers, and device manufacturers are less adept.[212] The FBI has trained investigators and powerful databases at its disposal; private companies only have publicly available information and the customer's word, and they are disincentivized from investigating at all. This point hardly merits elaboration.

To the extent that companies *do* investigate customers, a license system would remove much of these costs. Companies would not need to devote time and money to researching basic customer information. Instead, companies would focus on the more specialized task of

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[209] VENTER REPORT, *supra* note 99, at 17.

[210] *See, e.g.*, VENTER REPORT, *supra* note 99, at 12 (finding that while only 5% of orders to IGSC companies raise flags, the cost of investigating these is exorbitant for most companies); Diggans & Leproust, *supra* note 171, at 2 ("Twist Bioscience (a member company and officer of the IGSC) has witnessed first-hand how challenging some of the Guidance recommendations can become at increasing scale. Those difficulties must be surmounted while maintaining customer and sequence screening accuracy and still achieving the tight delivery timelines demanded by fierce competition within the global DNA synthesis industry").

[211] *See* 42 C.F.R. § 73.10.

[212] The 2022 HHS Guidance encourages all sellers (including gene synthesis providers, resellers, and device manufacturers) to know their buyer; know if the product contains sequences of concern, and if so, notify the customer; and if follow-up screening does not placate concerns about an order, report it to the FBI. *See* 2022 HHS Guidance, *supra* note 108, at 25497.

determining whether customers have good reasons for receiving flagged orders.

Concentrating this task into one government agency would be more efficient than having dispersed companies do it, each with a handful of scientists-turned-detectives. Since this is a matter of national security, it makes sense to give this task to the government.

C. Relative Advantage of Customer Verification

The biosecurity literature devotes much more attention to technical sequence screening solutions than customer verification.[213] This is unsurprising given that most contributors are scientists and technologists. But customer verification has a relative advantage over sequence screening, because technical advances are rendering sequence screening less effective and more expensive.[214]

Let us take a few examples. New synthesis techniques are making it easier to assemble genomes using smaller and smaller pieces (oligos), meaning we would need to screen vastly more sequences to keep up.[215] The advance of benchtop synthesis devices will allow more DNA to be printed in-house, instead of being ordered from synthesis companies, which will go unscreened unless something is done.[216]

One more extreme example to drill home the point. In addition to the four DNA bases that we learned about in biology (A, T, G, & C), scientists "have been expanding the language of DNA . . . by adding in new bases (S, B, P, and Z)."[217] There are four new letters and more to come! But if customers order sequences containing new bases, these

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[213] *But see* Diggans & Leproust, *supra* note 164, at 4 (arguing that the commandment to "know your customer" "should apply more broadly and explicitly to the entire synthetic biology industry and supply chain").

[214] *See* Center for Health Security, *supra* note 8, at 421 ("Since 2010, there have been technical advances that challenge or evade the biosecurity benefits of gene synthesis screening protocols. It is now more straightforward to assemble large pieces of genetic material using methods other than purchasing screened DNA synthesis products. . . Some of the most important advances that diminish the effectiveness of current gene synthesis screening approaches are Gibson Assembly, enzymatic assembly of DNA, genetic recoding, CRISPR, and a new type of desktop DNA synthesizer, a product that is just on the horizon").

[215] *See id.* at 421 ("Gibson Assembly is a widely used synthetic biology technique that can be used to rapidly and accurately assemble large genetic fragments from oligonucleotide fragments or from single-stranded or double-stranded DNA oligonucleotides. Using Gibson Assembly, smaller pieces of DNA (which are now unscreened) may be assembled to construct much larger fragments").

[216] *See id.* at 423. While less-capable oligo synthesizers have been around for decades, more capable gene synthesizers are gaining popularity and becoming more widespread.

[217] *See id.* at 422.

sequences "may be inscrutable to the gene synthesis provider."[218] Such "genetic recoding" means that customers could encrypt their orders, and sequence screening would need to decrypt it to be effective.[219]

The obvious lesson to draw is that it is easier to investigate the customer rather than decrypt the puzzle. I am not saying that technical sequence screening solutions are not worth thinking about; they are. But as sequence screening grows more difficult and provides less coverage, it becomes relatively more efficient to focus on the customer end.

While technology is progressing rapidly, people will stay the same. And whereas the biosecurity literature focuses on technical solutions, this essay aims for common sense.

D. Gap Filling

Verifying mystery customers is the most glaring gap. Under the self-regulation regime, some gene synthesis companies do nothing to verify their customers or do very little. A license regime would patch this hole by ensuring that customers pass a legitimacy test.

A license system would also go a long way toward correcting the venue-shopping problem. Like the legal analog, where lawyers file cases in, or transfer cases to, venues they perceive as advantageous, bad actors wishing to acquire dangerous pathogens can submit orders to the weakest link.[220] A license system would deter and weed out malicious actors from the start.

In the same vein, a license system would largely address the issue of circumvention—evading detection by ordering smaller bits of DNA from multiple manufacturers. Circumvention would be much less of a concern with an ex-ante license requirement because it would not be possible to fly totally under the radar.

A license requirement would even partially address the future problem of novel pathogen design. An individual would have to qualify for a license before they could order any DNA, including sequences that pose risks without raising alarms.

One can observe a common thread. A license regime creates an upfront barrier that would mitigate a host of bad downstream consequences.[221] If it was well built, it would stop most malicious

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[218] *Id.*
[219] *Id.*
[220] *See id.* at 425.
[221] A bonus is that it could provide a check on potentially irresponsible research. If a privately funded lab was studying a dangerous pathogen not on the FSAP list, it may be able to entirely evade federal oversight. *See* Ryan Ritterson et al., *A Call for a*

individuals that tried to climb over it.[222] And though it would be overly optimistic to say that it could never be scaled, the fact of its existence would deter many attempts to begin with.

VII. LICENSE REGIME ELEMENTS

Congress should pass a law creating the framework for a license regime. Like the FSAP, it should be administered by HHS and background checks should be performed by the FBI. This section takes a stab at the elements of a successful license system.

Much of this proposal is modeled after the FSAP, which has a sophisticated license architecture.[223] However, it avoids many of the FSAP's most burdensome attributes, which have engendered understandable scrutiny from the research community.[224] Many of the hoops from the FSAP approval process associated with dangerous pathogen research—like preparing a security plan, biosafety plan, and incident response plan—are inapplicable here.[225] Nor would licensed parties need to keep a running inventory of stock, "perhaps the most controversial element" of the FSAP because it is very hard to tally reproducing organisms.[226] Synthetic DNA is dead for the time being.

This proposal also borrows from the REAL ID Act, legislation that requires minimum identification standards to improve national

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National Agency for Biorisk Management, 20 HEALTH SEC. 2, 188 (2022). This could be true even if it were modifying the pathogen to make it more transmissible or more pathogenic, and even if researchers had a criminal background or a known association with terrorists. *Id*. To the extent the lab required synthetic DNA, a license regime would inject some scrutiny into the situation.

[222] *See also* Posner, *supra* note 64, at 524 ("one must also bear in mind that expenditures used to combat bioterrorism do more than prevent mega-attacks; the lesser attacks, which would still be very costly, both singly and cumulatively, would also be prevented").

[223] *See* 42 C.F.R. § 73.

[224] Even though the FSAP aimed not to unduly burden legitimate research, many believe it did just that. *See, e.g*., *Brighter Line*, supra note 29, at 20, 29–31 ("Paradoxically, the designation of these organisms and toxins as Select Agents put considerable burden on the scientific community to conduct this research while simultaneously adhering to costly and rigorous standards for security and accountability"); ENEMARK, *supra* note 31, at 55 (describing the "secure or stifle" tradeoff, and noting that after 2002 "there was a steep decline in the number of [scientific papers on the anthrax and ebola viruses] per million dollars of US government funding").

[225] *See* 42 C.F.R. §§ 73.7(g); 73.11; 73.12; 73.14. To handle Select Agents, there are additional hurdles that do not concern us here. These include "controlled access to facilities, physical security, inventory control, and site-specific risk assessments." *Brighter Line*, supra note 29 at 109.

[226] *Brighter Line*, *supra* note 29, at 23.

security.[227] Compliant licenses will soon be necessary to board federally regulated commercial aircraft, enter nuclear power plants, and access certain other federal facilities.[228] Whereas the REAL ID requirements will stretch to hundreds of millions of people traveling the skies, this is a more targeted approach.

A. License Requirement

The Select Agent regulations prohibit the possession, use, or transfer of Select Agents without a certificate of registration issued by the HHS Secretary.[229] So too here, the possession and use of synthetic biology materials (synthetic DNA/RNA and benchtop synthesizers) without a license would be prohibited, as would transferring them to an unlicensed party.[230]

B. Line Drawing

It is undesirable to draw too large of a circle. Licenses should be required for actors in the gene synthesis ecosystem, and ideally not be necessary for those who use synthetic DNA for other purposes such as PCR or gene sequencing. Happily, we have a rule of thumb to differentiate these purposes.

Remember, most single-stranded (oligo) sequences are ordered for PCR or sequencing, not for gene synthesis.[231] These orders tend to include sequences under 30 bases, whereas those used for gene synthesis are longer, between 40 and 60 bases.[232] Thus, it may make sense that a license requirement would only apply to DNA orders equal to or greater than 40 bases. This would avoid capturing an unnecessary segment of the synthetic DNA industry.

Admittedly, there is no bright line at forty bases.[233] It is still possible to synthesize genes with smaller pieces. Although this policy would be slightly over- and under-inclusive, it tries to strike a balance. A stricter policy would impose a license requirement on all synthetic DNA, regardless of length.

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[227] REAL ID Act of 2005, Pub. L. 109–13, Div. B (May 11, 2005). The Department of Homeland Security oversees its implementation.
[228] *Id.*
[229] 42 C.F.R. §§ 73.7(a); 73.16. Individuals and entities can also be exempted under § 73.5.
[230] *See id.*
[231] *See* VENTER REPORT, *supra* note 99, at 19–20.
[232] *See id.*
[233] *See id.*

C. Security Risk Assessment

Those seeking to do research with Select Agents must undergo a background check, called a "security risk assessment," by the FBI's Criminal Justice Information Services Division every three years.[234] Then the HHS Secretary must approve the individual or entity, the Responsible Official, and the individual who controls or owns the entity.[235]

This process tries to achieve "personnel reliability."[236] Under the Patriot Act, an application may be denied if the individual has been indicted or convicted of a crime punishable by imprisonment for greater than one year, has been dishonorably discharged from the military, is a fugitive from justice, is a current user of illegal drugs, has been committed to a mental institution, is illegally in the US, or is an alien national (not a lawful permanent resident) of a country officially designated as a state sponsor of terrorism.[237] To be clear, foreign nationals are eligible, as are those with mental illnesses that have voluntarily received treatment or been hospitalized.[238]

Under the Bioterrorism Act, an individual may also be denied if he is "reasonably suspected" of having committed certain crimes, been knowingly involved in a terrorist organization or an organization that commits crimes of violence, or is an agent of a foreign power.[239] Finally, an applicant can be denied if it is "necessary to protect the public health and safety," a catch-all provision.[240] Denied applicants may appeal.[241]

Arguably, the background check to receive a synthetic biology license should be less onerous than with FSAP because the risks are less direct. Researchers that work with dangerous pathogens pose a greater security risk than those that *could* build them, which still requires considerable skill.

As a floor, assessments should verify that applicants are who they say they are, confirm the basics of their identities, and acquire information about the types of work they perform.[242] This should be done

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[234] 42 C.F.R. § 73.10. Certificates used to be valid for five years, but this was decreased to three years in 2012. ENEMARK, *supra* note 31, at 52.
[235] § 73.7(d)(1).
[236] *See* RESPONSIBLE RESEARCH, *supra* note 58, at 47–48, 59.
[237] *Brighter Line*, *supra* note 29, at 20.
[238] RESPONSIBLE RESEARCH, *supra* note 58, at 47, 78.
[239] 42 C.F.R. § 73.8(a)(2).
[240] 42 C.F.R. § 73.8(a)(3), (4).
[241] 42 C.F.R. § 73.20.
[242] *See e.g.*, Department of Homeland Security, *REAL ID Requirements*, U.S. DEP'T HOMELAND SEC., https://www.dhs.gov/real-id/real-id-faqs ("At a minimum, you must

with overseas customers as well.[243] A more rigorous approach would aim for personnel reliability, using the criteria from FSAP. The lessons learned from its implementation should be applied.[244]

D. Responsible Official

Duplicating the "Responsible Official" approach from FSAP would further promote accountability.[245] Each licensed entity would need to designate a Responsible Official (or several) to ensure compliance.[246] Putting responsibility on their shoulders would foster ownership and incentivize careful monitoring.[247]

E. Chain-Linked Transactions

Every entity transferring synthetic biology materials would need to ensure that their counterpart had a valid license. This is particularly important because genetic materials and equipment often do not go straight from point A to point B.[248]

The 2022 HHS Guidance hopes that gene synthesis companies will verify the "end-user" of their products, but this is difficult when there are middlemen.[249] And again, companies are unlikely to go far out of

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provide documentation showing: 1) Full Legal Name; 2) Date of Birth; 3) Social Security Number; 4) Two Proofs of Address of Principal Residence; and 5) Lawful Status"); Maurer, *supra* note 69, at 22 ("Companies should also check shipping addresses to make sure that they correspond to registered businesses, internationally-recognized academic institutions, or similarly legitimate organizations").

[243] *See, e.g.*, Maurer, *supra* note 69, at 24 ("US and European gene synthesis companies find it prohibitively expensive to investigate customers in the developing world. Government can potentially fill this gap by investigating and licensing customers. Such a system would be similar to the 'Expert Traveler' lists currently found in US airports").

[244] *See generally* RESPONSIBLE RESEARCH, *supra* note 58, at 73–103 (recommending some changes to the personnel reliability process); *see, e.g.*, *id.* at 78 (recommending a broader appeal process for those denied for past criminal offenses).

[245] 42 C.F.R. §§ 73.7(c); 73.9.

[246] *Id.* §§ 73.7(c); 73.9.

[247] *See, e.g.*, *Biodefense Policy*, *supra* note 81, at 89, 92 = (recommending centralizing compliance activities in an institution); Rebecca L. Morvitz et al., *Promoting Biosecurity by Professionalizing Biosecurity*, 367 SCIENCE 6480, 856 (2020) (recommending a credentialing process to help address biosecurity gaps in their home institutions and collaborate with others at other institutions); *see* Kirsten X. Jacobsen et al., *Biosecurity in Emerging Life Sciences Technologies, A Canadian Public Health Perspective*, 2 FRONTIERS IN PUB. HEALTH 198, 1 (urging that labs be licensed and that a "qualified biological safety officer (BSO) would be designated for each institution.").

[248] Center for Health Security, *supra* note 8, at 425.

[249] *See* 2022 HHS Guidance, *supra* note 108; *see also* Sarah Carter & Diane DiEuliis, *Mapping the Synthetic Biology Industry: Implications for Biosecurity*, 17 HEALTH SEC. 5, 403, 405 (2019) ("[I]t is likely that many more synthetic biology companies

their way when it cuts into their bottom line. A simple solution is to require verification at every step.

This is similar to the FSAP's "chain of custody" requirement.[250] There, the CDC requires that transferring laboratories are registered and report each transfer.[251] So too here, the transferring parties should be required to verify that their counterpart is licensed and record the transaction. License security features can help prevent tampering and protect privacy.[252] Reporting transactions to the regulator seems excessive, except perhaps for sales of powerful synthesizers.

F. Records, Investigations, Revocation, & Notice

Each transfer would be recorded, and all licensees would be required to maintain a complete record for a certain duration. The FSAP requires that records be kept for three years, which seems to roughly balance accountability and hardship.[253]

As with the FSAP, investigations would help to catch violators before a catastrophe, and aid in attribution and prosecution efforts if something goes wrong.[254] The regulator would have the authority to conduct audits on suspected noncompliance without notice.[255]

If a party failed an investigation or audit, the regulator could revoke their license.[256] An appeal process would be available to rectify regulatory mistakes and abuses.[257]

And like the FSAP, licensees would be required to notify the authorities if synthetic biology materials were lost or stolen.[258]

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will be established, increasing the potential that the end user will be even further removed from the production of synthetic DNA.").

[250] *Brighter Line*, *supra* note 29, at 158.

[251] *Brighter Line*, *supra* note 29, at 109–10 (citing NRC 2009).

[252] *See* REAL ID Act of 2005, § 202(b)(8)-(9), 49 U.S.C. § 30301; Manoj Govindaiah, *Driver Licensing Under the REAL ID Act: Can Current Technology Balance Security and Privacy?, 2006* U. ILL. J.L. TECH. & POL'Y 201, 206–13 (2006).

[253] 42 C.F.R. § 73.17.

[254] *See Brighter Line*, *supra* note 29, at 23; *see also* RESPONSIBLE RESEARCH, *supra* note 58, at 52 (explaining that the FBI is automatically notified if an individual with a favorable security risk assessment is arrested or checked against databases).

[255] *See* 42 C.F.R. § 73.18. This could involve peeking at companies' logged records and copying them. If the authority wished, they could attempt a sting operation. Depending on the level of funding, the regime could also incorporate periodic or random audits.

[256] *Id.* at § 73.8.

[257] *Id.* at § 73.20.

[258] *See id.* at § 73.19.

G. Liability

Liability would be the backbone of a license regime, providing desired incentives and deterring and punishing noncompliance.

The FSAP allows the Inspector General of HHS to impose civil penalties,[259] and the Biological Weapons Act allows for criminal penalties.[260] If a *restricted* person possesses or transports Select Agents, they can face fines, imprisonment up to ten years, or both.[261] Criminal liability is lesser for an *unregistered* person; they can face fines, imprisonment up to five years, or both.[262]

Likewise, transfers of synthetic biology materials to restricted persons, and possession by restricted persons, should be criminalized. Providers and intermediaries can easily determine whether a customer is on a restricted list, so imposing criminal penalties would deter recklessness. Providing synthetic biology materials to someone for the purpose of developing a bioweapon is already criminalized.[263]

However, criminal penalties seem too punitive for transfers to or use by unregistered persons. As powerful as these technologies are, they pose a less direct threat to national security than complete pathogens. Significant civil penalties would likely be sufficient. Because noncompliance could range from a one-off mistake to a pattern of evasion, and as different players in the industry have varyingly deep pockets, penalties could be determined on a case-by-case basis by the HHS Inspector General. Another option is to predefine penalties as a fraction of entities' annual gross income. This would be persuasive to large corporations and avoid dooming startups.

H. Grace Period & Automatic Approvals

To achieve a smooth transition from the wild west to a license system, the law should include an ample grace period. It would likely take a few years to issue (and appropriately deny) a great number of licenses.[264]

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[259] *Id.* at § 73.21(a).
[260] 18 U.S.C. § 175b.
[261] *Id.* at § 175b(a).
[262] *Id.* at (b), (c).
[263] 18 U.S.C. § 175.
[264] For instance, the REAL ID Act was passed in 2005, but the enforcement date is May 7, 2025. *See REAL ID Frequently Asked Questions*, U.S. DEP'T OF HOMELAND SEC., https://www.dhs.gov/real-id/real-id-faqs (accessed Jan. 4, 2023). However, the grace period here should be much shorter since it involves far fewer licenses and no coordination with states.

Researchers who are already certified to work with Select Agents would automatically be approved, because another round of vetting would be redundant. The same could also apply to US government employees that have already undergone background checks.

I. Options: Red-Teaming and Tiers

Obviously, it should not be easy for a nefarious actor to obtain a license. The license regime should be stress-tested to make sure that it works. One way to do this is via red teaming—purposefully trying to exploit the system to make it stronger.[265] The government could partner with sophisticated white-hat actors to periodically reevaluate the system and patch holes.

Another feature of a license regime could be creating tiers based on different levels of risk.[266] Like the FSAP, which differentiate pathogens into several tiers based on their dangerousness and potential for misuse, the license regime could require greater or lesser burdens.[267] For instance, possessing a potent gene synthesizer may deserve heightened scrutiny.

Thus concludes my attempt to outline the basic elements of a license regime. These recommendations should be taken with a grain of salt; more input by scientists, lawyers, law enforcement and intelligence experts, and private companies would undoubtedly create a stronger product.[268]

VIII. COUNTERARGUMENTS

This section will consider the best arguments against a license regime and provide counterarguments. The chief complaint I anticipate

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[265] *See*, *e.g.*, Maurer, *supra* note 69, at 23 ("In the long run, it may also be important for customers to know when companies do not screen. This can be done by testing company systems with 'red team' orders for dangerous sequences. Government is the most natural provider for this kind of testing.").

[266] *See generally* Alexander Kelle, *Synthetic Biology and Biosecurity*, 10 EMBO REPORTS (2009) (describing how different synthetic biology subfields have different security implications).

[267] *See, e.g.*, DiEuliis et al., *supra* note 81, at 89 (noting that the FSAP regulations were updated in 2012 to include enhanced biosecurity measures for Tier 1 agents).

[268] *See also* Jesse Bloom, *A Plea for Making Virus Research Safer*, N.Y. TIMES (Oct. 30, 2022) ("Some virologists think we should have the final say, since we're the ones with technical expertise. I only partially agree. I'm a scientist. My dad is a scientist. My wife is a scientist. Most of my friends are scientists. I obviously think scientists are great. But we're susceptible to the same professional and personal biases as anyone else and can lack a holistic view. The French statesman Georges Clemenceau said, 'War is too important to be left to the generals.'").

is that it would constitute over-regulation. The argument from the other side is that it would be easily evadable and not worth the effort. Both are unpersuasive.

A. Overly Burdensome

Perhaps a license regime would just mire a prosocial industry in unnecessary red tape. Large US companies already screen sequences and we have no evidence that self-regulation has faltered. A license system would increase transaction costs, deter innovation, and dampen the burgeoning bioeconomy.

The "unnecessary" part of the argument is unpersuasive because companies' economic incentives direct against customer verification. I have endeavored to show that this investigative component is important and necessary. However, the added burden should be taken seriously.

The FSAP provides a useful point of reference. The stringency of these regulations may have hampered helpful research and deterred scientists from going down this road in the first place.[269] However, I have emphasized that the most burdensome aspects of the FSAP are not needed here. Written biosecurity and biosafety plans are unnecessary, as are running stocks of inventory. I have also argued that background checks should be less onerous because the risks are more attenuated.[270]

Even so, this proposal casts a wide net. Since synthetic DNA can be used for many purposes, it is difficult to craft an instrument that does not touch various industries that use it.[271] I have recommended that licenses only be required for synthetic DNA orders equal to or greater than forty base pairs to narrow its reach. It is also helpful that the customer base for synthetic DNA is currently "dominated by companies," which are easier to verify than individuals.[272]

As of 2009, the average turnaround time for a security risk assessment in FSAP was only a month.[273] During the initial phase when many assessments were needed, the wait time was only two months.[274]

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[269] *See* ENEMARK, *supra* note 31, at 55; *Brighter Line*, *supra* note 29, at 24; DiEuliis, *supra* note 81, at 94.
[270] One implication might be that license holders only need to renew their license every five years instead of every three years, as in the FSAP.
[271] These industries include pharmaceuticals, chemicals, fuels, agriculture, food, materials, and consumer products. Carter & DiEuliis, *supra* note 250, at 404.
[272] *See id.* at 405. A decade ago, the field was dominated by individual researchers in academic settings.
[273] RESPONSIBLE RESEARCH, *supra* note 58, at 48.
[274] *Id.* at 48–49.

Here, a generous implementation period could help ensure that companies are not halted in their tracks and would minimize downsides.

What if greater securitization deters the next Steve Jobs from going into biology? Well, if Steve is seriously interested, he will be willing to jump through a few hoops to pursue his dreams. A more serious answer is that our open access approach is unsustainable as dual-use biotechnology keeps improving.

The emerging bioeconomy will be overwhelmingly good for society. Innovations will improve medicine, energy, and agriculture. But since biotechnology can be misused, it would be a mistake to continue our *laissez-faire* approach. We must try to strike a balance between innovation and security.[275] A moderate investment to curb the risk of potentially catastrophic bioterrorism is money well spent.

B. Ineffective Security

Conversely, one might worry that a license system would not provide meaningful security or deterrence. Nefarious individuals could sneak through the license approval process, bribe or threaten license holders, or order synthetic DNA from abroad.

It goes without saying that a license regime should be as bulletproof as possible. I have shown that background checks by the FBI are preferrable to those by private companies, who are incentivized not to do them. Red teaming could help find and patch weaknesses.

Licenses would not annul the benefits of sequence screening; they would provide an additional layer of defense. To the extent that companies verify customers, they would no longer need to investigate basic information, though they should still have in-house experts examine DNA orders that raise flags and contact customers to interrogate their purpose.

Of course, a well-resourced actor with firm intentions could still acquire dangerous materials from overseas. But as the world leader in biotechnology, the US arguably has an obligation to be the first mover. Doing so would give it leverage to encourage security efforts elsewhere, including China, which aims to become the new frontrunner in synthetic

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[275] *See also* Executive Order, *supra* note 4, at 2 ("Simultaneously, we must take concrete steps to reduce biological risks associated with advances in biotechnology. We need to invest in and promote biosafety and biosecurity to ensure that biotechnology is developed and deployed in ways that align with United States principles and values and international best practices, and not in ways that lead to accidental or deliberate harm to people, animals, or the environment.").

biology.[276] International solutions could include revamping the Biological Weapons Convention or writing a new multilateral treaty, creating a new international organization, or simply exercising soft power and developing norms. If the US acts first and exerts tactical pressure, it can reduce global risks.[277]

CONCLUSION

Dual-use biotechnology is a moving target. Any regulatory solutions are fraught with uncertainty and impervious to straightforward cost-benefit analysis.[278] But these difficulties should not breed inaction. The synthetic biology self-regulation regime must give way.

The US should require that gene synthesis companies screen the DNA sequences they provide to help prevent facile misuse. It should also implement a license regime to help verify customers and ensure their legitimacy. As biotechnologies become cheaper and even more powerful, it is hard to imagine a desirable future where anyone can get their hands on synthetic DNA and the machines that make it.

Though gene synthesis security efforts are not a panacea, preventing gene synthesis materials from being "easily and directly misused" is a goal worth achieving.[279]

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[276] *See* Center for Health Security, *supra* note 8, at 427; REPORT TO CONGRESS OF THE U.S.-CHINA ECONOMIC AND SECURITY REVIEW COMMISSION 8 (Nov. 2021). China passed its first comprehensive biosecurity law in 2021, but it is too early to know its implications. *See* Huigang Liang et al., *Significance of and Outlook for the Biosecurity Law of the People's Republic of China*, J. OF BIOSAFETY AND BIOSECURITY 3, 46–50 (2021).

[277] *See also* Jonathan B. Wiener, *The Diffusion of Regulatory Oversight*, in THE GLOBALIZATION OF COST-BENEFIT ANALYSIS IN ENVIRONMENTAL POLICY 128 (Michael A. Livermore & Richard L. Revesz, eds., Oxford Univ. Press, 2013) (internal citations omitted) ("legal scholars came to appreciate that legal evolution also occurs through the exchange of legal concepts across legal systems via borrowing, also called "hybridization."").

[278] *See* Daniel A. Farber, *Uncertainty*, 99 GEO. L.J. 901, 903, 946–49 (2011).

[279] *See* Gigi K. Gronvall, *Safety, Security, and Serving the Public Interest in Synthetic Biology*, 45 J. OF INDUS. MICROBIOLOGY & BIOTECHNOLOGY 463, 464–65 (2018).