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SYNTHETIC BIOLOGY AND BIOSAFETY GOVERNANCE IN THE EUROPEAN UNION AND THE UNITED STATES

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ABSTRACT

This article examines how synthetic biology, which is the construction of novel biological parts, devices, and systems, as well as the modification of regular organisms, impacts biosafety regimes in the European Union (EU) and the United States (US). The article examines the nature and benefits of synthetic biology. It then reviews associated biosafety challenges, before analysing the suitability of governance frameworks in the EU and the US in dealing with these challenges. Based on this analysis, the article contends that, despite some similarities with older technologies, synthetic biology is essentially novel. Consequently, it undermines existing biosafety regimes in both jurisdictions. The article advocates for effective governance, combining formal regulation and self-governance, in addition to the global coordination of governance measures. This will help maintain an agile policy and curtail any regulatory loopholes. This article fosters awareness on the existence of many unresolved controversies over the synthetic biology technology.

Keywords: synthetic biology, biosafety, EU, US

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BIOLOGI SINTETIK DAN GOVERNAN BIOKESELAMATAN DI KESATUAN EROPAH DAN AMERIKA SYARIKAT

ABSTRAK

Artikel ini mengkaji bagaimana biologi sintetik, iaitu pembuatan dan modifikasi bahagian-bahagian biologi yang baharu, peralatan dan sistem memberi impak kepada prinsip berjaga-jaga dan perundangan berkaitan dengan governan biokeselamatan di Kesatuan Eropah dan Amerika Syarikat. Artikel ini membincangkan sifat dan faedah biologi sintentik. Seterusnya, ia mengulas cabaran kerangka biokeselamatan di Kesatuan Eropah dan Amerika Syarikat. Hasil dari analisis ini, artikel ini mencadangkan bahawa walaupun terdapat persamaan dengan teknologi terdahulu, biologi sintetik pada hakikatnya adalah baharu. Pada hakikatnya, ia melemahkan rejim biokeselamatan dalam kedua-dua negara. Artikel ini mendukung tadbir urus efektif yang menggabungkan peraturan formal dan tadbir urus kendiri, selain daripada koordinasi global langkah-langkah tadbir urus. Ia memberi kesedaran bahawa masih terdapat banyak kontroversi melibatkan biologi sintetik, membantu dasar yang cerdas dan mengurangkan lompang perundangan.

Kata kunci: biologi sintetik, biokeselamatan, Kesatuan Eropah, Amerika Syarikat.

INTRODUCTION

Driven by high-throughput Deoxyribonucleic Acid (DNA) sequencing, synthesis and amplification technologies of the last three decades,[1] synthetic biology involves the ground-up design and construction of novel biological parts, devices and systems, as well as the modification of regular organisms[2] for societal needs. Despite

[1] European Commission's Directorate-General for Health and Consumers, "Synthetic Biology: From Science to Governance" (March 18-19, 2010). Accessed April 22, 2018, https://www.ec.europa.eu/health/dialogue.../synbio_workshop_report_en.pdf.

[2] Royal Academy of Engineering (RAE), "Synthetic Biology: Scope, Applications and Implications" (May 6, 2009). Accessed February 17, 2018, https://www.raeng.org.uk/publications/reports/synthetic-biology-report.

these benefits, there are simultaneous concerns over the biosafety of this technology. This article examines this opposing dimension of the technology. It first examines the nature and benefits of synthetic biology. At this stage an assessment of the extent of its novelty, compared to earlier established technologies, notably genetic engineering or GE, is done. From here, the article continues to review the associated challenges before analysing the suitability of biosafety governance in the EU and the US for those challenges.

This article submits that, while synthetic biology partly converges with earlier established technologies, especially GE, it exhibits many unique attributes, which on the whole, render it revolutionary. Consequently, it unravels pre-existing EU and US biosafety legal regimes. This leaves a "regulatory free zone" for some synthetic biology players and activities.

Governments should adapt existing governance measures and develop new ones to meet the novelty of synthetic biology. Formal regulation should combine with responsible self-governance by professional and amateur synthetic biologists, as well as other stakeholders. Given the crossborderness of synthetic biology, with numerous players and varying backgrounds, this governance system should be coordinated globally for maximum effectiveness. To manage new challenges, it should be reviewed consistently as the technology evolves.

While the current literature mostly focuses on the benefits of synthetic biology, this article recalls its flip side and reawakens debates about unresolved controversies surrounding the technology. It attempts to challenge claims that synthetic biology is not different from GE and that existing GE regulations suffice. By maintaining the focus on synthetic biology debates, this article helps to keep governments informed and curtail regulatory gaps.

THE NATURE OF SYNTHETIC BIOLOGY

According to the central dogma of molecular biology, all living things are regulated by a chemical called DNA. The DNA encodes genes

that direct intergenerational transfer of genetic information[3] and determine physical appearance, as well as behaviour of living things.[4] It has four nucleotide base pairs: adenine (A), thymine (T), guanine (G) and cytosine (C). A always pairs with T and C with G to form complimentary base pairs joined together by sugar-phosphate backbones.[5]

The four letters, A, B, C and D, constitute the DNA alphabet. A combination of any three letters forms a word, called codon, which denotes an amino acid or a signalling function.[6] A particular number and sequence of amino acids encodes a specific protein[7] and proteins support cellular processes. Scientists believe that, like electrical and electronic engineering constructs, biological cells are composed of hierarchically arranged parts,[8] which can be rearranged to reprogram cells for user-defined functions.[9] This conviction inspired the design of model biological systems on computers.[10] Those models are then physically constructed and systematically refined in conventional laboratories, using synthetic genes[11] created from chemicals by gene synthesis companies.[12] Those developments laid the foundation for synthetic biology.[13] Inspired by the belief that life can be calculated

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3 René Fester Kratz, *Molecular and Cell Biology for Dummies* (Hoboken, NJ: Wiley Publishing Inc., 2009), 209-229.

4 Ibid., 101.

5 Ibid.

6 Oliver Morton, "Life Reinvented," *Wired Mag.* (January 1, 2005). Accessed March 6, 2019, http://www.wired.com/2005/01/mit-3/.

7 Andrew W. Torrance, "Synthesizing Law for Synthetic Biology," *Minn. J. L. Sci. & Tech*. 11 (2010): 644.

8 D. Ewen Cameron et al., "A Brief History of Synthetic Biology," *Nat. Rev. Microbiol.* 12(2014): 381, 386.

9 Ibid., 381.

10 A. Ribarits et al., "Synthetic Biology" (2014), 35-36, www.bmg.gv.at/cms/home/.../synthetic_biology_02122014_final.pdf.

11 David W. Ehrhardt and Wolf B. Frommer, "New Technologies for 21st Century Plant Science," *Plant Cell* 24 (2012): 389.

12 ETC Group, "Extreme Engineering. Report. Map of Commercial DNA Synthesis Companies" (2007)**,** 8-9. Accessed March 14, 2018, https://www.cbd.int/doc/emerging-issues/etcgroup-introduction-synthetic-biology-2011-013-en.pdf.

13 Ibid.

and mirrored through computer models,[14] synthetic biology is concerned with the design and construction of standard biological parts, devices and systems from chemicals,[15] as well as the modification of regular organisms with biological parts for useful functions.[16] Biological parts are genetic sequences serving as building blocks for novel devices and systems.

Synthetic biologists employ two main research approaches, top-down and bottom-up. In the top-down approach, the genomes of natural organisms, especially bacteria, are serially reduced, leaving only genes essential for survival.[17] Specific genetic sequences can be added to this minimal genome, also called chassis, regulating it to function as desired.[18] Like computer software, those sequences encode instructions directing the chassis, as hardware, to discharge a specific function.[19] Using this approach, the J. Craig Venter Institute (JCVI) trimmed the genome of the *Mycoplasma genitalium* bacterium to its essential minimum.[20] Only about 387 of its 482 genes proved essential for survival, in addition to 43 structural Ribonucleic Acid (RNA) genes.[21] Synthetic biology's top-down approach is comparable to earlier established technologies, such as traditional biotechnology, metabolic engineering and GE, which similarly involve the modification of regular organisms to produce metabolites more

[14] Jane Calvert, "The Commodification of Emergence: Systems Biology, Synthetic Biology and Intellectual Property*," Biosocieties* 3 (2008): 391.

[15] RAE, "Synthetic Biology," 13.

[16] Ibid.

[17] Matthias Heinemann and Sven Panke, "Synthetic Biology-Putting Engineering into Biology," *Syst. Biol.* 22 (2006): 2793.

[18] Rik Parens et al.*, "*Ethical Issues in Synthetic Biology: An Overview of the Debates," (24 June 2009), 7, www.synbioproject.org/publications/synbio3/.

[19] Ernesto Andrianantoandro et al., "Synthetic Biology: New Engineering Rules for an Emerging Discipline," *Mol. Syst. Biol.* 2 (2006):1.

[20] John I. Glass, et al., "Essential Genes of a Minimal Bacterium," *PNAS* 103 (2006): 425.

[21] *Ibid.*, 429. See also Daniel G. Gibson et al., "Complete Chemical Synthesis, Assembly and Cloning of a Mycoplasma Genitalium Genome," *Science* 319 (2008): 1215, 1219.

efficiently. Particularly, similar principles underlie synthetic biology and GE such that both are often indistinguishable.[22]

Nonetheless, key differences exist. The bottom-up approach, for example, is more radical than GE, although still at an embryonic stage. More than mere modification of regular organisms, it involves the design and creation of organisms from scratch. Standard biological parts are combined in a bottom-up manner to form novel devices and systems expected to function like regular cells.[23] Structurally, those systems may still be modelled on regular cells, such as the four standard nucleotide base pairs,[24] as well as normal cellular processes. Scientists at JCVI created the world's purportedly first self-replicating cell, using this approach. The cell's genome was designed after that of the 1.08 million-base pair *M. mycoides* bacterium.[25] It was then chemically produced and transferred into the empty cell of *M. capricolum* bacterium. The synthetic genome remodelled and completely regulated this host cell, thereby creating a self-replicating cell; a "synthetic" organism called *M. mycoides*.[26]

That feat surpasses GE in which only one or just a few natural genes are transferable between regular organisms. The above two approaches aside, synthetic biologists plan to engineer protocells;[27] synthetic cells that can host minimal genomes as quasi production factories[28] for functionally novel proteins.[29] Their structures and processes may differ from those of regular cells. They may, for

[22] S.R. Carter et al., "Synthetic Biology and the US Biotechnology Regulatory System" (May 2014), 7, 9, https://www.jcvi.org/synthetic-biology-and-us-biotechnology-regulatory-system-challenges-and-options.

[23] RAE, "Synthetic Biology," 21-22.

[24] Ibid.

[25] Ibid.

[26] D.G. Gibson et al., "Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome," *Science* 329 (2010): 52-55.

[27] Anthony C. Forster and George M. Church, "Toward Synthesis of a Minimal Cell," *Mol. Syst. Biol.* 45 (2006): 1-8.

[28] Maureen A. O'Malley et al., "Knowledge-Making Distinctions in Synthetic Biology," *Bioessays* 30 (2007): 57-59.

[29] Ibid*;* Gerald F. Joyce, "Toward An Alternative Biology," *Science* 336 (2012): 307-308.

example, be regulated by more than four nucleotide base pairs[30] or by unnatural acids, such as Xenonucleicacids (XNAs), instead of natural DNAs.[31] These last two approaches are usually called orthogonal biology[32] and xenobiology.[33]

Remarkably, unlike GE practised by well-funded, professional scientists, synthetic biology is open, with little financial constraints, to novices, including Do-It-Yourself biology (DIYbio) groups and students through the International Genetically Engineered Machine (iGEM) competition.[34] In contrast with GE experiments restricted to standard laboratories with biosafety protocols,[35] synthetic biology experiments are undertaken in personal kitchens, garages and open fields; synthetic organisms are grown in ponds, lakes, lagoons and fermentation tanks.[36] Additionally, this technology professes open innovation, unlike GE which is characterised by secrecy and closed innovation.[37]

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[30] Y. Zhang et al., "A Semi-synthetic Organism that Stores and Retrieves Increased Genetic Information," *Nature* 551 (2017): 644-647 (reporting expansion of the four regular nucleotide base pairs to six).

[31] For creation of Xenonucleic acids capable of evolution, see Vitor B. Pinheiro et al., "Synthetic Genetic Polymers Capable of Heredity and Evolution," *Science* 336 (2012): 341-344.

[32] Markus Schmidt and Lei Pei, "Synthetic Toxicology: Where Engineering Meets Biology and Toxicology," *Toxicol. Sci.* 120 (2011): 212.

[33] Manuel Porcar and Juli Pereto, "Are We Doing Synthetic Biology?," *Syst. Synth. Biol.* 6 (2012): 82.

[34] Torrance, "Synthesizing Law for Synthetic Biology," 634.

[35] E.g., *WHO Laboratory Biosafety Manual* (Geneva: WHO, 2004); NIH, "Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules" (15 April 2016), https://osp.od.nih.gov/wpcontent/uploads/NIH_Guidelines.html.

[36] The International Civil Society Working Group on Synthetic Biology (ICSWGSB), *A Submission to the Convention on Biological Diversity's Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) on the Potential Impacts of Synthetic Biology on the Conservation and Sustainable Use of Biodiversity* (October 17, 2011), 20. Accessed November 11, 2018, https://www.cbd.int/doc/.../Int-Civil-Soc-WG-Synthetic-Biology-2011-013-en.pdf; Carl Safi et al., "Morphology, Composition, Production, Processing and Application of Chlorella Vulgaris: A Review," *Renew. Sust. Energ. Rev.* (2014): 268.

[37] G. Seyfried, L. Pei and S. Markus, "European do-it-yourself (DIY) Biology: Beyond the Hope, Hype and Horror", *Bioessays* 36 (2014): 548.

BENEFITS OF SYNTHETIC BIOLOGY

Synthetic biology enables many previously impossible experiments addressing diverse societal needs. Current applications include synthetic yeast that produces antimalaria drug compound, artemisinin, at faster, cheaper rates than plant-based production,[38] as well as synthetic algae that convert biomass into biofuels[39] and oils.[40] Microbes have also been engineered to live in the human body as nutrients, disease sensors and therapeutics. When introduced into probiotic yogurt, for example, those microbes can supply nutrition, scan the human gut for diseases and discharge synthetic gene circuits as treatment.[41] Another noteworthy application of synthetic biology is the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technique. It facilitates more accurate gene editing in cheaper and faster ways than older gene editing molecular tools like zinc finger endonucleases.[42]

Other applications of synthetic biology include yeast for more efficient production of flavonoids like vanilla used in domestic baking and beer brewing,[43] as well as bacteria for more sustainable supply of

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[38] Dae-Kyun Ro et al., "Production of the Antimalarial Drug Precursor Artemisinic Acid in Engineered Yeast," *Nature* 440 (2006): 940-943; Mark Peplow, "Malaria Drug Made in Yeast Causes Market Ferment: Synthetic Biology Delivers Combination Therapies into an Uncertain Market," *Nature* 494 (2013): 160.

[39] Biotechnology Industry Organization, "Current Uses of Synthetic Biology for Renewable Chemicals, Pharmaceuticals and Biofuels" (2013), 4-5. Accessed November 27, 2018, https://www.bio.org/sites/default/files/Synthetic-Biology-and-Everyday-Products-2012.pdf.

[40] Asha Parmar et al., "Cyanobacetria and Microalgae: A Positive Prospect for Biofuels," *Bioresource Technol.* 102 (2011): 10163.

[41] W.C. Ruder, T. Lu and J.J. Collins, "Synthetic Biology Moving into the Clinic," *Science* 333 (2011):1248-1252; Food and Environment Research Agency (FERA), *Final Report. Synthetic Biology: Prospective Products and Applications for Food and Feed - Requirements for Regulation* (April 9, 2014), 11. Accessed April 16, 2015, https://www.food.gov.uk/.../872-1-1616_Synthet.

[42] Heidi Ledford, "CRISPR, the Disruptor," *Nature* 522 (2015): 20.

[43] N.A. Bahaudin et al., "Current Progress in Production of Flavonoids Using Systems and Synthetic Biology Platforms," *Sains Malaysiana* 47 (2018): 3077-3078, 3081.

coenzyme Q10 food supplement normally produced in limited quantity through yeast fermentation.[44] In the aesthetic sector, a synthetic version of the cosmetics ingredient, squalane, has been engineered.[45] Moreover, attempts have been made to engineer ornamental glowing plants.[46] Engineering of luminous trees serving as street lights and plants serving as reading lamps, is also contemplated.[47]

BIOSAFETY CHALLENGES OF SYNTHETIC BIOLOGY

Despite its benefits, synthetic biology threatens biosafety. This part of the article highlights these dangers.

Invasive species

Bacteria can invade open algae ponds and novel algae species may emerge, threatening biodiversity.[48] For closed systems like

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[44] FERA, *Final Report,* 11; D. Scott et al., *Potential Positive and Negative Impacts of Components, Organisms and Products resulting from Synthetic Biology Techniques on the Conservation and Sustainable Use of Biodiversity, and Associated Social, Economic and Cultural Considerations,* Part I of Synthetic Biology, Technical Series No. 82 (2015), 23. Accessed February 4, 2019, https://www.cbd.int/ts/cbd-ts-82-en.pdf.

[45] Katie Nichol, "Amyris Has Teamed Up with France-based Cosmetics Ingredients Company, Soliance, to Produce Synthetic Squalane, an Emollient and Moisturizing Ingredient Used as a Protective Agent in Cosmetics" (23 June 2010), http://www.cosmeticsdesign-europe.com/Formulation-Science/Soliance-partners-with-Amyris-to-produce-renewable-squalane.

[46] Andrew Pollack, "A Dream of Trees Aglow at Night," *The N.Y. Times* (May 7, 2013). Accessed October 19, 2018, F:\SB A POLLACK A Dream of Glowing Trees Is Assailed for Gene Tinkering The New York Times.html.

[47] Pollack, "A Dream of Trees Aglow at Night."

[48] G.E. Marchant, "Evaluation of Regulatory Framework for Algae and Cyanobacteria Engineered to Produce Transportation Fuels" (November 23, 2011), 6. Accessed January 27, 2018, www.jcvi.org/cms/...regulatory.../marchant.pdf.

bioreactors, human errors,[49] faulty reactors,[50] earthquakes or floods[51] can cause accidental release.[52] Intentional release can even occur through sabotage. Upon escape into the environment, synthetic organisms may be irretrievable.[53] Their survival and reproductive potentials, as well as likely impacts on humans, animals, plants and the environment, are unforeseeable.[54] Organisms engineered with distinctive metabolic and control mechanisms are novel life forms[55] with poorly understood characteristics.[56]

Even if such organisms prove weaker than natural ones,[57] brief spells in the environment could cause significant damage.[58] Organisms engineered for biofuels can excrete such products uncontrollably upon escape from containment.[59] Some may mutate and acquire unexpected longevity, rendering them more dangerous to

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[49] A. Leonard, "ETC Group Warns Against "Bio-error. Self-regulation by Scientists is not Sufficient for a Technology that is as Potentially Disruptive as Synthetic Biology," *Salon* (January 19, 2007). Accessed, March 6, 2019, http://www.salon.com/2007/01/19/etc_responds_to_endy/.

[50] Ribarits et al., "Synthetic Biology," 61.

[51] ICSWGSB, *A Submission to the SBSTTA*, 19.

[52] B. Parent, "Reproduction-powered Industry: Coordinating Agency Regulations for Synthetic Biology," *N.C. J.L. & Tech.* 15 (2014): 313.

[53] G.V. Dana et al., "Synthetic Biology: Four Steps to Avoid a Synthetic-Biology Disaster*," Nature* 483 (2012): 29.

[54] FERA, *Final Report. Synthetic Biology*, 19.

[55] A. Griffin, "Scientists Create New Life Form in a Lab, Altering the Fundamentals of DNA," *The Independent Online* (January 24, 2018). Accessed June 17, 2018, https://www.independent.co.uk/news/science/dna-life-form-new-a-t-c-g-x-y-scripps-research-institute-synthetic-semi-a7544056.html.

[56] K. Pauwels et al., "Risk Assessment Challenges of Synthetic Biology," *J. Consum. Protect. & Food Safety* 8 (2013): 224.

[57] V. De Lorenzo, "Environmental Biosafety in the Age of Synthetic Biology: Do We Really Need a Radical New Approach? Environmental Fates of Microorganisms Bearing Synthetic Genomes Could be Predicted from Previous Data on Traditionally Engineered Bacteria for In Situ Bioremediation," *Bioessays* 32 (2010): 926-931.

[58] Carter et al.,*"*Synthetic Biology and the US Biotechnology Regulatory System," 40.

[59] Marchant, "Evaluation of Regulatory Framework for Algae and Cyanobacteria," 21.

natural ecosystems through novel gene transmission.[60] Organisms meant for intentional releases may be engineered to survive harsh environments, thus increasing potential threat levels.

Risks from synthetic biology residues

Cells from microbes used for fuel production could survive and multiply in the environment when disposed with residues.[61] Live bacteria and DNA have reportedly escaped into the environment from untreated residues and laboratory sinks, hybridising with wild species.[62] This has resulted in unexpected survival and dispersal of transgenes.[63] In the US, a Pfizer employee became ill after exposure to an engineered virus due to poor laboratory containment.[64] Between 1979 and 2004, about 1,448 laboratory infections reportedly occurred, causing 36 fatalities.[65]

Risks from microbial drugs

Live microbes ingested as drugs pose novel biosafety risks. Conventionally, drug products, not the organisms generating them, are consumed. The byproducts are diluted after metabolism in the human system before being discharged into the environment with hardly any risk.[66]

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[60] O. Wright, G. Stan and T. Ellis, "Building-in Biosafety for Synthetic Biology," *Microbiol.* 159 (2013): 1222.

[61] Marchant, "Evaluation of Regulatory Framework for Algae and Cyanobacteria," 21.

[62] Markus Schmidt and Victor de Lorenzo, "Synthetic Constructs in/for the Environment: Managing the Interplay between Natural and Engineered Biology," *Febs Lett.* 586 (2012): 2200.

[63] Ibid.

[64] Andrew Pollack and Duff Wilson, "A Pfizer Whistle-Blower is Awarded $1.4 Million," *The N.Y. Times* (April 2, 2010). Accessed March 17, 2018, http://www.nytimes.com/2010/04/03/business/03pfizer.html.

[65] Andrew Pollack and Duff Wilson, "Safety Rules Can't Keep Up With Biotech Industry," *The N.Y. Times* (May 27, 2010). Accessed March 17, 2018, http://www.nytimes.com/2010/05/28/business/28hazard.html.

[66] J. Paradise and E. Fitzpatrick, "Synthetic Biology: Does re-writing Nature Require Re-writing Regulation?" *Penn. St. L. Rev*. 117 (2012): 61.

An organism consumed as a drug is not digested but survives in the human body. Preventing its escape into the environment or tracing it, upon escape, would be problematic.[67] Being alive, it can survive and multiply, endangering the environment. It can even invade and administer undesired treatment in another human system.[68]

Unpredictability of biological systems

Biological systems are unpredictable. In a previous study, the bacterium, *Klebsiella planticola*, engineered to enhance wheat fermentation into ethanol, survived when released into laboratory soil and killed natural microbes, as well as wheat plants by producing ethanol with their roots.[69] In another study, a mousepox virus engineered to serve as contraceptive for mice, unexpectedly turned virulent, exterminating the entire experimental group exposed to it and half the control group vaccinated against it.[70]

Those studies demonstrate the unpredictability of biologically engineered systems. However well-characterised, biological parts, once combined into devices and systems, may result in unpredictable behaviour.[71] Such unpredictability will increase as organisms are

[67] Ibid.

[68] Ibid.

[69] M. E. Holmes et al., "Effects of Klebsiella planticola SDF20 on Soil Biota and Wheat Growth in Sandy Soil," *Appl. Soil. Ecol.* 11 (1999): 67-78.

[70] Ronald J. Jackson et al., "Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox," *J. Virol.* 75 (2001): 1205-1209.

[71] Adam P. Arkin and Daniel A. Fletcher, "Fast, Cheap and Somewhat in Control," *Genome Biol.* 7 (2006): 3.

engineered from more diverse genetic components[72] or modified by eliminating some of their natural components.[73]

Liberalisation of synthetic biology and "bioerrors"

Information technology and companies providing cheap gene synthesis services liberalise synthetic biology for amateurs. They can design genetic sequences on personal computers[74] and electronically order their synthesis for under US $ 0.30 per base pair.[75] The open source philosophy of the BioBricks Foundation, Registry of Standard Biological Parts and iGEM strengthens amateur participation by freely disseminating biological parts.[76] Those parts can be assembled into devices and systems having biosafety implications.

Through DIYbio groups, which now spread across Asia, Australasia, Europe and North America,[77] amateurs also have access to significant genetic information. The DIYbio website, DIYbio.org, allows members to freely exchange information for assorted synthetic biology constructs, some for personal treatment.[78] Many DIYbio

[72] Diane O. Fleming, "Risk Assessment of Synthetic Genomics: A Biosafety and Biosecurity Perspective," Working Papers for Synthetic Genomics: Risks and Benefits for Science and Society (2006), 105-106. Accessed February 23, 2018, http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics report/CommissionedPapers-Synthetic-Genomics-Governance.pdf.

[73] Denise Caruso, "Synthetic Biology: An Overview and Recommendations for Anticipating and Addressing Emerging Risks," *Sci. Prog.* (2008): 5-6.

[74] A. Pollack, "How Do You Like Your Genes? Biofabs Take Orders," *The N.Y. Times* (September 12, 2007). Accessed November 23, 2018, http://www.nytimes.com/2007/09/12/technology/techspecial/12gene.html ?pagewanted=print&_r=0.

[75] Catherine Jefferson et al., "Synthetic Biology and Biosecurity: Challenging the 'Myths'," *Front. Public Health* 2 (2014): 6.

[76] Parent, "Reproduction-powered Industry," 315-316.

[77] Alison McLennan and Matthew Rimmer, "Inventing Life; Patent Law and Synthetic Biology," *The Conversation* (February 27, 2012). Accessed March 9, 2018, http://theconversation.com/inventing-life-patent-law-and-synthetic-biology-5178.

[78] Parent, "Reproduction-powered Industry," 317.

group members lack training in biology[79] or standard biosafety procedures.[80] They may not know and, therefore, not comply with laws regulating their activities, some of which may require prior risk assessment and regulatory approval.[81]

BIOSAFETY GOVERNANCE

Informal biological measures and formal biosafety regulations have been adopted in response to the challenges of synthetic biology.

Informal (biological) measures

In response to the biosafety challenges associated with their activities, synthetic biologists are adopting informal measures. They are augmenting physical confinement of synthetic organisms with biological measures.[82] These include fitting them with "seat belts" to prevent escape into the environment and interaction with wild species.[83] Organisms are engineered with modified genetic codes that render them incapable of survival in the wild without nutrition available only in laboratories.[84] Those orthogonal systems cannot tranfer or receive genes because, unlike regular organisms, they cannot interprete genetic instructions.[85] Another biosafety device is genetic "kill switch," which automatically triggers the secretion of

[79] Bryan G. Norton, "Synthetic Biology: Some Concerns of a Biodiversity Advocate. Remarks on Synthetic Biology to the Presidential Commission on Bioethics" (September 13, 2010), 3. Accessed November 12, 2018, *bioethics.gov/.../...*Presidential Commission for the Study of Bioethical Is.

[80] Ribarits et al., "Synthetic Biology," 66-67.

[81] Carter et al., "Synthetic Biology and the US Biotechnology Regulatory System," 41, 45.

[82] A.A. Snow and V.H. Smith, "Genetically Engineered Algae for Biofuels: A Key Role for Ecologists," *Bioscience* 62 (2012): 1222-1223.

[83] K. Xue, "Synthetic Biology New Menagerie, Life Reengineered*," Harvard Mag.* (September-October, 2014), 47. Accessed December 29, 2018, collinslab.mit.edu/files/0914-42.pdf.

[84] Gerd H.G. Moe-Behrens et al., "Preparing Synthetic Biology for the World," *Front. Microbiol*. 4 (2013): 2.

[85] M. Schmidt, "Xenobiology: A New Form of Life as the Ultimate Biosafety Tool," *Bioessays* 32 (2010b): 322-331.

proteins that are lethal to cells when exposed to specific chemicals.[86] Although worthwhile, these informal measures have limitations. Given the nascency of synthetic biology, scientists do not yet know many of the associated problems,[87] the "unknown unknowns."[88] They can, therefore, not preempt them.

Moreover, microbes may circumvent "kill switches" through mutation.[89] Microbes engineered to die upon escape into the wild without essential metabolites may still survive due to the unexpected availability of such material or by simply parasiting on regular organisms.[90] Even if they die, their DNA could survive and be scavenged by wild species.[91] Efforts to contain synthetic organisms by genetically recoding them or fitting them with artificial DNAs, while promising, remain work-in-progress.[92] Orthogonal systems may not be completely isolated from natural species. Alternative nucleic acids with unique backbones or letters could still bond with natural DNA or RNA, thereby producing toxic effects that impede DNA replication and normal gene expression.[93]

Formal regulation

Current legal frameworks in the EU and the US that are relevant to biosafety are usually considered adequate for the challenges of synthetic biology. How well they respond to those challenges is, however, questionable since they largely predate this technology. This part of the article continues with an analysis of existing EU and US biosafety regulations in order to determine their efficacy in dealing with those novel challenges.

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86 Xue, "Synthetic Biology New Menagerie," 47.

87 Ibid.

88 Dana et al., "Synthetic Biology: Four Steps to Avoid a Synthetic-Biology Disaster," 29.

89 Schmidt and de Lorenzo, "Synthetic Constructs in/for the Environment," Biology," 2200-2201.

90 Wright, Stan and Ellis, "Building-in Biosafety for Synthetic Biology," 1228.

91 Moe-Behrens et al., "Preparing Synthetic Biology for the World," 4.

92 Schmidt and de Lorenzo, "Synthetic Constructs in/for the Environment," 2203.

93 Moe-Behrens et al., "Preparing Synthetic Biology for the World," 6.

EU biosafety regulations

In a pre-Brexit report on the adequacy of existing rules for the evaluation of prospective synthetic biology products in the UK, the Food and Environmental Research Agency (FERA) observes overlaps between GE and synthetic biology.[94] Thus, laws governing Genetically Modified Organisms (GMOs) and Genetically Modified Microorganisms (GMMs) in the EU, of which the UK had been a member, apply to synthetic biology. Similarly, a report prepared for the Federal Ministry of Health in Austria, another EU member, concludes that, given similarities between GE and synthetic biology, existing GE regulations largely cover synthetic biology products.[95]

Potentially applicable EU laws include Directive 2001/18/EC on the deliberate release of GMOs and Directive 2009/41/EC on the contained use of GMMs. Pertinently, the EU follows a precautionary, process-based policy entailing a rigorous risk assessment of GE products before regulatory approval.[96] Under Directive 2001/18/EC, GMOs mean, *organisms, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination*, and organism means, *any biological entity capable of replication or of transferring genetic material*. Directive 2009/41/EC defines GMM as, *microorganism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination*, and microorganism means, *any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including viruses, viroids, and animal and plant cells in culture.*

Those definitions cover synthetic biology constructs and two applications mentioned earlier in this article can be used to illustrate the applicability of both directives. Directive 2009/41/EC can cover the manufacturing process for coenzyme Q10 when being purified from the microbe,[97] while Directive 2001/18/EC can govern the use

[94] FERA, *Final Report*, 6.
[95] Ribarits et al., "Synthetic Biology," 65.
[96] Carter et al., "Synthetic Biology and the US Biotechnology Regulatory System," 15, 32, 34.
[97] FERA, *Final Report*, 14.

of vanilla as flavonoid in home-made beer, since the living engineered yeast will eventually be released into the environment.[98]

REGULATORY CHALLENGES

Despite the coverage of the EU directives, synthetic biology products can be produced in and imported from non-EU countries lacking comparable safety standards and requisite intelligence to effectively track products.[99] While suggestions that GE regulations suffice for synthetic biology hinge on the supposed overlap of both technologies, synthetic biology constructs could be more radically transformed and intricate than those of GE.[100] Consequently, GE regulations would become ineffective.[101] Current GMO risk assessment frameworks are unsuitable to assess, monitor and detect synthetic microbes in the wild due to uncertainty over their survival and reproductive patterns in varying environmental conditions.[102]

Additionally, existing guidelines for the deliberate release of GMMs are essentially untested.[103] Given the novelty and greater complexity of synthetic biology constructs, designing appropriate risk assessment procedures would be cumbersome and time-consuming, especially where no natural comparators exist.[104] Plants subjected to substantial genetic modification, for example, are incomparable to conventional ones due to changes in their constitution and metabolic processes.[105]

Those engineered with synthetic genes will exhibit significant biological, metabolic and physiological variations, making them even more difficult to compare with natural plants.[106] This will be more so

[98] Ibid., 21.
[99] FERA, *Final Report*, 15.
[100] Carter et al., "Synthetic Biology and the US Biotechnology Regulatory System," 4-5.
[101] Ibid.
[102] FERA, *Final Report*, 19; J. L. Martinez and F. Baquero, "Mutation Frequencies and Antibiotic Resistance," *Antimicrob. Agents Chemother.* 44 (2000): 1771.
[103] FERA, *Final Report*, 20.
[104] Ibid., 19.
[105] Ribarits et al., "Synthetic Biology," 54.
[106] Ibid.

for organisms having expanded nucleotides or XNA instead of DNA. The risk of unnatural off-target effects aside,[107] such organisms lack progenitors and, therefore, comparators.[108] Probiotic bacteria, for instance, demonstrate how synthetic biology may challenge current risk assessment procedures. The bacteria will live in a consumer's gut interacting with other microbes. Some of those microbes are endogenous, while others are ingested through foods that may also introduce noxious substances that can be transformed detrimentally by the gut or other gut microbiota.[109] Assessing and identifying risk in the intricate interactions within that gut environment in each individual consumer with varying food intake patterns will be problematic.[110] This challenge extends to microbes expected to live in the human system as drugs without being digested.

Other challenges of synthetic biology for GE regulations in the EU include how, for example, to monitor the degree of deliberate release and environmental impact of vanilla produced from engineered yeast when used as flavonoid in home-made beer;[111] whether deliberate release can even be said to have occurred once the product is sold to consumers;[112] and whether recent gene implantation techniques like cisgenesis, intragenesis, as well as epigenesis are covered by the definition of genetic modification under Directive 2001/18/EC and, therefore, GMO regulations.[113]

It is also unclear whether vanillin produced from engineered yeast can be labelled as *natural*.[114] Clarification on whether engineered products can be labelled as natural is vital because current EU law considers a product as natural, only if derived directly from vegetable material.[115] Nonetheless, some view vanillin as natural, since it is

[107] National Academies of Sciences, Engineering and Medicine (NASEM), *Preparing for Future Products of Biotechnology* (Washington DC: National Academies Press, 2017), 112, 118.
[108] Norton, "Synthetic Biology: Some Concerns of a Biodiversity Advocate," 4-5.
[109] FERA, *Final Report*, 23.
[110] Ibid.
[111] Ibid., 21.
[112] Ibid.
[113] Ibid., 32.
[114] Ibid., 8.
[115] Ibid.

produced by engineered yeast; a living organism not present in the end product.[116]

US biosafety regulations

Similar to the EU, current GE regulations in the US are considered adequate for most safety, health and environmental impacts of synthetic biology.[117] Nonetheless, unlike the EU's precautionary approach, the US regulatory system focuses on a product's unique characteristics, not the technological means of production.[118] It considers GE products to be substantially equivalent to and as safe as natural ones.[119] Thus, the health and environmental risks of GE products are viewed as similar to those of natural counterparts.[120] Foods modified with nucleic acids, for example, are not considered to present special risks because such genetic materials are also found in consumable natural plants and animals.[121] Therefore, a product does not warrant stricter regulation than a natural equivalent simply because it is derived from GE or synthetic biology.[122]

[116] Erika Check Hayden, "Synthetic-biology Firms Shift Focus," *Nature* 505 (2014): 598.

[117] Presidential Commission for the Study of Bioethical Issues (PCSBI), *New Directions. The Ethics of Synthetic Biology and Emerging Technologies* (16 December 2010), v, 8.

[118] J. Kuzma and A. Kokotovich," Renegotiating GM Crop Regulation," *Embo Rep*. 12 (2011): 884-885.

[119] 21 C.F.R. § 170.30 (2005); Paul R. Mayers et al., "The Concept of Substantial Equivalence" in Keith T. Atherton (ed.) *Genetically Modified Crops: Assessing Safety* (London: Taylor & Francis, 2002), 63-64, n.1.

[120] Earle Nestmann et al., "The Regulatory and Science-Based Safety Evaluation of Genetically Modified Food Crops. A US Perspective" in Keith T. Atherton (ed.) *Genetically Modified Crops*, 3.

[121] US Food and Drug Administration, Statement of Policy: Foods Derived from New Plant Varieties, Federal Register 57: 22984–23005 (1992); NASEM, *Preparing for Future Products of Biotechnology*, 82.

[122] Carter et al., "Synthetic Biology and the US Biotechnology Regulatory System," 15, 18.

Coordinated framework

In the Coordinated Framework for the Regulation of Biotechnology of 1986,[123] three main departments are assigned as coordinated agencies to administer the US regulatory system for biotechnology, constituted by the Food, Drug and Cosmetic Act, Federal Insecticide, Fungicide and Rodenticide Act and Plant Protection Act. The Coordinated Framework concluded that new regulations or regulatory agencies were unnecessary for GMOs.[124]

Pursuant to the Food, Drug and Cosmetic Act (FDCA),[125] the Food and Drug Administration (FDA) oversees the quality and safety of foods, including animal foods and feeds, food additives, dietary supplements, human and veterinary drugs, cosmetics, tobacco and their GE equivalents.[126] Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA),[127] the Environmental Protection Agency (EPA) is charged with human health and environmental protection.[128] It evaluates new microbes, plant or microbial pesticides and new applications of known pesticides, to ensure that they are environmentally safe. It also regulates GMMs based on its authority to regulate, *new chemical substances* under the Toxic Substances Control Act (TSCA).[129] Pursuant to the Plant Protection Act (PPA),[130] the US Department of Agriculture (USDA), along with its subsidiary units, particularly the Animal and Plant Health Inspection Service (APHIS), evaluates the safety of growing plants. This is to protect

[123] US Office of Science and Technology Policy, 1986; 1 Fed. Reg. 23,302 (1986) as modified by Modernizing the Regulatory System for Biotechnology Products: Final Version of the 2017 Update to the Coordinated Framework for the Regulation of Biotechnology (January 4, 2017). Accessed June 15, 2018, https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/2017_coordinated_framework_update.pdf.

[124] 51 Fed. Reg. 23,306 (1986).

[125] 21 USC. § 342(a)(1) and 21 USC. § 348.

[126] K.A. Isham, "Caveat Venditor: Products Liability and Genetically Modified Foods," *J. Food L. & Pol'y.* 2 (2006): 92.

[127] 7 USC. § 136(a).

[128] Isham, "Caveat Venditor," 91.

[129] 15 USC. § 2601 *et seq*., as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act, P.L. No. 114-182 (22 June 2016).

[130] 7 C.F.R Part 340.

other plants from diseases, plant pests or potential plant pests.[131] Therefore, it regulates field trials of GE plants.[132]

Regulatory challenges - Food and Drug Administration (FDA)

Under the US regulatory system, natural and GE foods, dietary supplements and cosmetics are marketable without prior safety approval, although the FDA can recall them from the market, if found to endanger human health and safety.[133] Producers can consult the FDA for premarket review, but this is voluntary.[134] Some DIYbio producers, who are unfamiliar with the regulatory system, may not even indulge in consultations.[135]

Based on the above explanation, consumable probiotic bacteria can be marketed without approval, if considered as foods.[136] If viewed as food additives, then under the National Environmental Policy Act (NEPA),[137] regulatory assessment of their health and environmental implications must precede commercialisation.[138] Arguably, synthetic microbes producing coenzyme Q10 food supplement or squalane for cosmetics can be marketed without regulatory approval.[139] This is because the US generally does not regulate products based on the technological means of production. The most that could be done is the recalling of the product from the market, if found to threaten human or animal health. Such products would require premarket approval, only if the engineering process introduces a new substance or one that significantly exceeds the level normally present in natural foods.[140]

[131] 7 USC. §§ 7701 *et seq*.
[132] Carter et al., "Synthetic Biology and the US Biotechnology Regulatory System," 16.
[133] Ibid., Box C, 19, 20,
[134] Ibid., 18 n. 11, 19, 42.
[135] NASEM, *Preparing for Future Products of Biotechnology*, 83-84.
[136] Carter et al., "Synthetic Biology and the US Biotechnology Regulatory System," 42.
[137] 42 U .S .C . § 4321 *et seq*.
[138] Carter et al., "Synthetic Biology and the US Biotechnology Regulatory System," 42.
[139] Ibid.
[140] S. Bar-Yam et al., "The Regulation of Synthetic Biology: A Guide to United States and European Union Regulations, Rules and Guidelines," SynBERC and iGEM Version 9.1 (January 10, 2012), 9. Accessed March

Determining whether a synthetic biology technique produces that technical effect and who makes this determination, however, remain opaque issues.[141]

Dietary ingredients marketed in the US after 1994, raise even more safety issues. Producers must give the FDA a 75-day notice together with evidence of safety, but commercialisation can proceed, if the FDA takes no decision before that notice expires.[142] This highlights the regulatory challenges the coordinated agencies would face without adequate resources.[143] For human and veterinary drugs, pesticides and food additives, safety approval must precede commercialisation.[144]

The concept of substantial equivalence, which underpins the US regulatory system, is opposed by advocates of a precautionary policy.[145] They argue that the Coordinated Framework, which conceived that concept, was introduced, without thorough assessment of potential risks, which were still poorly understood during its adoption.[146] For synthetic biology products, the likely risks are more unpredictable, considering the degree of novelty and intricacy of the underlying technology. Studies have proven that GE regulations have

17, 2018, www.synberc.org/.../Concise%20Guide%20to%20Synbio%20Regulation; Lynn Bergeson et al., "Leveraging Synthetic Biology's Promise and Managing Potential Risk. Are We Getting It Right?" (October, 2015), 14. Accessed February 4, 2018, http://www.synbioproject.org/events/leveraging-synthetic-biologys-promise/.

[141] Bergeson et al., "Leveraging Synthetic Biology's Promise and Managing Potential Risk," 14.

[142] NASEM, *Preparing for Future Products of Biotechnology*, 82.

[143] Ibid.

[144] Carter et al., "Synthetic Biology and the US Biotechnology Regulatory System," 18- 23.

[145] Friends of the Earth et al., "The Principles for the Oversight of Synthetic Biology" (March 13, 2012), 1, 3, 13. Accessed March 9, 2019, www.synbioproject.org/.../principles_for_the_oversight_of_synthetic_biology.

[146] Gregory N. Mandel, "Gaps, Inexperience, Inconsistencies, And Overlaps: Crisis in the Regulation of Genetically Modified Plants and Animals," *WM. & Mary L. Rev.* 45 (2004): 2258.

been inadequate in dealing with the risks of GE products,[147] making them even less effective in dealing with the more complicated constructs of synthetic biology. Additionally, since conventional foods, food supplements and cosmetics require no premarket risk assessment, synthetic biology equivalents would similarly be exempted, whereas their likely effects on consumers are unknown. The FDA can order withdrawal of such products from the market, but only if they prove harmful to human or animal health; it cannot act where environmental safety is threatened.[148] Further, for synthetic microbes, once released, recalling them would be difficult, if found to endanger human health or the environment.[149]

In the near future, instructions received through DIY kits may enable domestic production of products normally made in standard factories, particularly probiotics, cosmetics, sprays and liquids. These products may elude regulation since they are not intended for interstate commercialisation, distribution or shipment.[150] In terms of risk analysis, determining the type of environmental release or exposure to such products would be more problematic, compared to those manufactured in standard settings and regulated under the FDCA.[151]

Product labelling is another likely challenge. The FDA only requires labelling for synthetic foods having lower nutritional quality than natural equivalents.[152] Thus, synthetic vanillin and other foods may not require labelling and disclosure of production method, if deemed as nutritionally equivalent to natural ones.[153] Labelling would be necessary, only if quality and safety concerns exist, but the FDA

[147] A. Malatesta et al., "A Long-Term Study on Female Mice Fed on a Genetically Modified Soybean: Effects on Liver Ageing," *Histochem. Cell Biol*. 130 (2008): 967-977; Zinatul A. Zainol et al., "Mandatory Labelling of Genetically Modified (GM) Foods," *Int. Environ. Agreements* 15 (2013): 205.

[148] Carter et al., "Synthetic Biology and the US Biotechnology Regulatory System," 28, 42.

[149] Friends of the Earth et al.,"The Principles for the Oversight of Synthetic Biology," 6.

[150] NASEM, *Preparing for Future Products of Biotechnology,* 111.

[151] Ibid.

[152] P.B. Hutt, R.A. Merrill and L.A. Grossman, *Food and Drug Law: Cases and Materials* (St. Paul, Minnesota: Foundation Press, 2014).

[153] NASEM, *Preparing for Future Products of Biotechnology,* 81.

will bear the burden of proof.[154] Similarly, it is unsettled whether synthetic squalane can be described as *natural* or whether cosmetics produced from it can be labelled in the same way as conventionally produced ones, without amounting to misbranding[155] in violation of the FDCA.[156] Ultimately, consumers may not know exactly what they are consuming.

US Department of Agriculture (USDA)

As for APHIS, synthetic biology plants will likely challenge its authority to regulate field trials of plants qualifying as *regulated article*. A GE organism is a regulated article, if engineered from an organism or agent meeting the definition of a plant pest or an unclassified organism or one without a classification or where the GE organism is determined to be a plant pest or one which there is reason to believe is a plant pest.[157]Apparently an exception to the general rule that the US does not regulate products based on the technological means of production, those plants require APHIS' approval, which normally contains conditions aimed at preventing the escape of transgenes from test sites.[158] After field trials, APHIS must be requested to *deregulate*, meaning to certify such plants as unlikely to present plant pest threats, before they can be marketed.[159]

Nonetheless, through synthetic biology, plants exhibiting new characteristics can be engineered, without using plant pests, thereby taking them outside the meaning of *regulated article*.[160]

[154] US Food and Drug Administration, "Statement of Policy: Foods Derived from New Plant Varieties," Federal Register 57: 22984–23005 (1992); *Alliance for Bio-integrity et al. v. Donna Shalala, et al*. No. Civ. A. 98-1300 (CKK). United States District Court, District of Columbia (2000).

[155] Bergeson et al., "Leveraging Synthetic Biology's Promise and Managing Potential Risk," 23.

[156] 21 USC. § 343(c).

[157] 7 CFR 340.1.

[158] Carter et al., "Synthetic Biology and the US Biotechnology Regulatory System," 25.

[159] Ibid.

[160] Emily Waltz, "Tiptoeing Around Transgenics," *Nat. Biotechnol.* 30 (2012): 215-217.

Consequently, APHIS cannot review them for environmental risks.[161] In 2010, APHIS confirmed that it lacked authority to review a synthetic bioluminescent plant engineered by BioGlow because it was not a regulated article as no plant pests were used.[162] BioGlow marketed that plant without undergoing an environmental risk assessment.

The DIYbio outfit, TAXA Biotechnologies (TAXA), similarly evaded regulation by not using plant pests.[163] They modified their glowing plant with a gene gun, instead of *Agrobacterium tumefaciens*, popularly used for gene implantation, which would have qualified the product as a plant pest.[164] As with BioGlow, APHIS confirmed that TAXA's glowing plant was not a regulated article.[165] It, therefore, did not supervise the cultivation or distribution of those seeds.
Although TAXA's glowing plant project eventually failed,[166] project donors and pre-order customers were to receive the engineered

[161] T.E. Bundy, "APHIS Authority to Regulate Plants Modified Using Synthetic Biology" (December 22, 2011), 1, 9. Accessed April 10, 2019, https://s3.amazonaws.com/org.jcvi.s3-www-drupal/s3fspublic/assets/projects/synthetic-biology-and-the-us-regulatory-system/bundy.pdf.

[162] See APHIS' letter to Dr. Alexander Krischevsky entitled, "APHIS Confirmation of the Regulatory Status of Genetically Engineered Plants Developed by BioGlow" (March 13, 2013), 1. Accessed August 9, 2018, https://www.aphis.usda.gov/.

[163] Emily Waltz, "GM Grass Eludes Outmoded USDA Oversight," *Nat. Biotechnol.* 29 (2011): 772.

[164] L. Zeldovich, "Glow-in-the-dark Plants Go on Sale, *Fox News* (March 27, 2014), Accessed June 18, 2018, http://www.foxnews.com/science/2014/03/27/glow-in-dark-plants-go-on-sale.htm.

[165] See APHIS' letter to Mr. Anthony Evans entitled, "Re: Request for Confirmation of the Regulatory Status of Transgenic Bioluminescent *Arabidopsis thaliana"* (December 23, 2014), 1-2. Accessed April 3, 2018, https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated/Regulated_Article_Letters_of_Inquiry.

[166] *Wired Mag.*, "Inside the Glowing-plant Startup That Just Gave Up its Quest (April 4, 2017). Accessed November 14, 2017, https://www.wired.com/story/inside-the-glowing-plant-startup-that-just-gave-up-its-quest/.

seeds.[167] How the plant would have affected recipients, wild plants or animals that ever fed on it, is unclear.[168] Donors of, at least, US$250 qualified for a *DIY maker kit* containing information and ingredients to individually transform their plant.[169] That transformation required the use of *A. tumefaciens.* Thus, any transformed plant would have qualified as a plant pest, warranting APHIS's regulatory review, just as interstate transfer of plant seeds would have required prior EPA notification.[170] However, DIY kit recipients may not have appreciated this and, therefore, not have complied with those legal obligations.[171]

Unsupervised environmental release of the glowing plant seeds departed from existing policy subjecting most GE plants to field trials, after APHIS' approval.[172] Although plants eluding APHIS' oversight, such as food crops, are still subject to FDA's regulation and import controls,[173] unsupervised releases undermine environmental protection against the risks of synthetic biology plants.[174] TAXA insisted that their plant was engineered to self-destruct in the wild,[175] but Friends of the Earth and biotechnology watchdog, ETC Group, feared genetic drift through interbreeding with natural species.[176] Further concerns were that the glowing plant project was a frivolous application of synthetic biology and future,

[167] Glowing Plant, "Updates on the Glowing Plant and Synthetic Biology News" (November 12, 2015). Accessed July 27, 2017, http://blog.glowingplant.com/.

[168] Bergeson et al., "Leveraging Synthetic Biology's Promise and Managing Potential Risk," 45.

[169] Ibid.

[170] Ibid.

[171] NASEM, *Preparing for Future Products of Biotechnology,* 94.

[172] Carter et al., "Synthetic Biology and the US Biotechnology Regulatory System," 27.

[173] Waltz, "GM Grass Eludes Outmoded USDA Oversight," 773.

[174] Bundy, "APHIS Authority to Regulate Plants Modified Using Synthetic Biology," 7.

[175] E. Callaway, "Glowing Plants Spark Debate. Critics Irked Over Planned Release of Engineered Organism," *Nature* 498 (2013): 15-16.

[176] *CBC News*, "Plant Seeds Expected to Ship in December. Biohackers' Genetically Engineered Glow-in-the-Dark Plant Attracts Fans and Critics*"* (October 9, 2014). Accessed March 7, 2018, http://www.cbc.ca/news/technology/glowing-plant-seeds-expected-to-ship-in-december-1.2794138Plant seeds expected to ship in December.

perhaps more risky ones, could likewise be undertaken, without regulation.[177] The USDA has subsequently confirmed that it would also not regulate plants engineered with CRISPR,[178] amidst controversies over potential off-target effects.[179] How such products would be received outside the US is uncertain.

Environmental Protection Agency (EPA)

Synthetic biology GMMs will question EPA's regulatory authority. The agency focuses on intergeneric microbes, defined as microbes involving gene transfer between organisms of different taxonomic genera.[180] It views them as potentially more risky since they incorporate genes from widely unrelated organisms.[181] Yet, genes from microbes can be altered or radically modified into unnatural sequences through synthetic biology and then replanted into them. Since neither case involves intergeneric transfer, EPA may lack regulatory authority, whereas the modified microbes could exhibit characteristics with higher likelihood of risk than those of intergeneric ones.[182]

[177] Ibid.

[178] USDA Press, "Secretary Perdue Issues USDA Statement on Plant Breeding Innovation" (March 28, 2018). Accessed May 10, 2018, https://www.usda.gov/media/press-releases/2018/03/28/secretary-perdue-issues-usda-statement-plant-breeding-innovation.

[179] J. Kuzma and A. Kokotovich, "Renegotiating GM Crop Regulation," *Embo Rep.* 12 (2011): 884-885; A. Pollack, "A Powerful New Way to edit DNA," *The N.Y. Times* (March 3, 2014). Accessed February 23, 2018. http://www.nytimes.com/2014/03/04/health/a-powerful-new-way-to-edit-dna.html?_r=0.

[180] EPA, Microbial Products of Biotechnology; Final Regulations under the Toxic Substances Control Act; Final Rule, 62 Fed. Reg. 17,910, 17913 (1997); 40 C.F.R. § 725.3(2)(v) (2013).

[181] Marchant, "Evaluation of Regulatory Framework for Algae and Cyanobacteria," 10.

[182] Ibid., 11; Gregory N. Mandel, "Managing Risks of Synthetic Biology: Assessing the US Regulatory System. Microbes Engineered for Chemical Production or Bioremediation" (2012). Accessed January 23, 2018, http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-biologyand-the-us-regulatory-system/mandel.pdf.

Moreover, intergenerics are regulated only if they are distributed or commercialised, meaning that the TSCA may not cover those made and used solely at home.[183] Other regulatory challenges are likely from GMMs such as CRISPR-engineered mosquitoes. Apart from off-target effects, that is, potentially adverse unintended modification, these complicated constructs have no comparators and, therefore, no established risk assessment procedure or regulatory path.[184] Further, since GMMs must undergo pre-approval field trials, they can escape into the environment with more lasting impacts, given their ability to mutate and reproduce. This is unlike conventional chemicals, which impact is usually limited to the finite amounts used in field trials.[185]

Other regulatory challenges

The above challenges aside, synthetic biology plants or GMMs, which are not regulated by any of the coordinated agencies may present dilemma to university researchers. The National Institute of Health (NIH) funding guidelines forbid them from conducting field trials of laboratory engineered organisms, without approval from a coordinated agency.[186] Unsupervised testing will violate those guidelines and possibly deprive researchers of future funding. This could deter them from otherwise beneficial field experiments.[187] By contrast, DIYbio groups can undertake such experiments since NIH guidelines do not bind them.[188] The liberalisation of synthetic biology increases the likelihood of many such unsupervised experiments.[189]
Open releases of synthetic biology products may activate other statutes, such as the US Endangered Species Act (ESA). This seeks to control how the actions of federal regulatory agencies impact endangered species.[190] The Act requires them to consult with relevant

[183] NASEM, *Preparing for Future Products of Biotechnology,* 95.
[184] Ibid., 118, 139-140, 172.
[185] Marchant, "Evaluation of Regulatory Framework for Algae and Cyanobacteria," 12.
[186] Carter et al., *"*Synthetic Biology and the US Biotechnology Regulatory System," 40-41.
[187] Ibid*.*, 41.
[188] Ibid*.*
[189] Mandel, "Managing Risks of Synthetic Biology," 5.
[190] Section 7(a)(2), Endangered Species Act (1973).

bodies, including the National Marine Fisheries Service (NMFS) and the Fish and Wild Life Service (FWS). Yet, such consultations have been rare.[191] For example, despite its authority to bar importations of species capable of endangering humans, wildlife and agriculture,[192] the FWS did not participate in the field release of Oxitec mosquitoes,[193] which would be examined shortly. Lack of familiarity with ESA consultation process may expose the actions of the coordinated agencies to legal challenge for non-conformity with the Act.[194]

Synthetic biology is also likely to create problems of overlap and conflict within and between regulatory agencies. Oxitec mosquitoes exemplify this problem. Oxitec, which engineered those mosquitoes to control wild *Aedes aegypti*, claimed that they were meant for use as pesticide, but their ultimate purpose was clearly human disease control.[195] It was difficult deciding whether field testing of the mosquitoes should be handled by the FDA's Center for Veterinary Medicine (CVM) as a new animal drug or by the agency's Center for Drug Evaluation and Research (CDER) or its Center for Biologics Evaluation and Research (CBER).

Previously, CDER or CBER regulated antimalarial drugs produced by synthetic biology organisms, but not where the organisms are used to control the vectors of that disease. [196] The FDA eventually decided to regulate the mosquitoes as a new animal drug under CVM's supervision, but they were clearly also regulable as a human drug[197] and even by EPA as a pesticide under FIFRA.[198] Understandably, Friends of the Earth insisted that the test was a medical trial bound by legal requirements safeguarding human

[191] NASEM, *Preparing for Future Products of Biotechnology,* 98-99.
[192] 18 USC. § 42 Lacey Act.
[193] NASEM, *Preparing for Future Products of Biotechnology,* 99.
[194] *Institute for Fisheries Resources et al. v. Burwell et al*. Case No. 3:16-cv-01574, US District Court for the Northern District of California (2016); NASEM, *Preparing for Future Products of Biotechnology,* 99.
[195] Bergeson et al., "Leveraging Synthetic Biology's Promise and Managing Potential Risk," 3.
[196] Ibid., 17.
[197] Ibid., 20.
[198] 40 C .F .R . § 152 .15(a)-(c); Bergeson et al., "Leveraging Synthetic Biology's Promise," 20.

subjects, such as the informed consent of test area inhabitants.[199] Apart from regulatory authorities, those uncertainties also affect product developers, who need clarity on the correct regulatory path for their products and related legal requirements.[200]

Besides the Coordinated agencies, the Consumer Product Safety Commission (CPSC) and the Occupational Safety and Health Administration (OSHA) may also have to regulate synthetic biology products, but the Coordinated Framework does not clarify their functions.[201] They may lack appropriate regulatory authority, manpower and expertise for prompt and effective evaluation of risks associated with future, more complex synthetic biology products designed for use in diverse settings.[202] Since the safety of such products, particularly chemicals, may depend on intended uses and users' experience, new safety challenges may arise, especially in workplaces.[203] For OSHA, which is responsible for controlling exposure to hazardous chemicals and other substances in workplaces, such challenges may be aggravated because, in situations of uncertainty, it bears the burden of proving risk.[204]

The Coordinated Framework does not even sufficiently address consumer and occupational safety concerns that would likely intensify as new applications of synthetic biology emerge.[205] Where, for example, DIYbio products like the glowing plants fall outside the competence of regulatory agencies, hardly any authority exists under existing consumer safety laws for the agencies to control their distribution, sale and use so as to protect users or other individuals

[199] Friends of the Earth, Issue Brief. "Genetically Engineered Mosquitoes in the US" (undated), 3. Accessed April 9, 2018, www.foe.org/system/storage/877/df/1/959/Issue_brief_GE_mosquitoes_in_USpdf.

[200] Bergeson et al., "Leveraging Synthetic Biology's Promise and Managing Potential Risk," 20.

[201] NASEM, *Preparing for Future Products of Biotechnology,* 6.

[202] Ibid., 86-88, 99-100.

[203] A.C. Lin, *Prometheus Reimagined: Technology, Environment and Law in the Twenty-first Century* (Ann Arbor: University of Michigan Press, 2013).

[204] *Industrial Union Department, AFL-CIO v. American Petroleum Institute* 448 US 607 (1980).

[205] NASEM, *Preparing for Future Products of Biotechnology,* 68.

from harm arising from their use.[206] Shortage of manpower will impose further regulatory constraints on CPSC, OSHA and the coordinated agencies. Within EPA, plant pathologists, soil scientists, fisheries biologists and agricultural engineers are dwindling in numbers.[207] Finally, the complexity of the Coordinated Framework, itself, creates uncertainty for innovators, particularly DIYbio groups, as well as consumers, and may erode public confidence in the regulation of future applications of synthetic biology.[208]

Comparing the EU and US approaches

From the foregoing discussion, some comparisons can be made between the biosafety regimes of the EU and the US. Obviously, both aspire to protect the health of humans, animals, plants and the general environment. Nonetheless, as already noted, the EU's regulatory system is process-based and takes a more precautionary approach. Although elements of this are present in the US regulatory system, as seen in the PPA, the latter is essentially product-based and more *reactive* in nature. Each system has implications for health safety. The former may delay research relevant to the protection of health, while with the latter, product risks may become apparent only after damage to society. Further, given the philosophy underlying the Coordinated Framework, the US lacks specific regulations for GMOs and emerging technologies similar to the EU's overarching directives. This often causes uncertainty over the applicability of existing legislation, such as the TSCA and PPA, to the safe regulation of synthetic biology.[209]

Noticeably, the US system involves diverse regulatory agencies, as well as public consultations. Although this study shows a need for still more coordination among US regulatory agencies, the existence of multiple agencies generally permits interagency coordination to

[206] Ibid., 73.
[207] Ibid., 124.
[208] Ibid., 6.
[209] Benjamin D. Trump, "Synthetic Biology Regulation and Governance: Lessons from TAPIC for the United States, European Union and Singapore," Health Policy 121 (2017): 1140.

minimise gaps and overlaps.[210] This and the wider scope for participation improve the quality of biosafety regulation and enable the review of regulations to address new scientific developments.[211]At the same time, greater participation may complicate and slow down the regulatory system, as well as its reform.[212] Further, the typically litigious character of the US system, with a tendency to resolve regulatory disputes through litigation, may impinge upon the joint governance of synthetic biology for biosafety.[213] Unlike the US multiagency regulatory system, the EU equivalent is more centralised and principally under the charge of the Directorate-General XI (Environment). This limits possibilities for interagency coordination seen in the US. In addition to that, given its centralised nature, reforming the regulatory system to capture new scientific evidence relevant to biosafety tends to be slower than in the US, where the Coordinated Framework has been revised several times.[214] Nevertheless, there is generally consultation among government, researchers, businesses and civil society in the EU on how best to achieve biosafety, although views divide on whether this is more the case there or in the US.[215] Moreover, while all EU members are required to implement EU biosafety-related Directives, they do so using their discretion. Consequently, the quality of implementation may vary among states, some of which may also adopt more stringent standards than EU minimum requirements. In respect of product labelling, the US tends to be permissive, while the EU adheres to stricter labelling rules. With a permissive labelling scheme, consumers may not know what they are consuming, even when they

[210] Lee Ann Patterson and Tim Josling, "Regulating Biotechnology: Comparing EU and US Approaches," (2005), 7. Accessed April 10, 2020, https://www.researchgate.net/publication/29991058_Regulating_biotechnology_comparing_EU_and_US_approaches_European_Policy_Papers_8.

[211] Ibid.

[212] Trump, "Synthetic Biology Regulation and Governance," 1142.

[213] Ibid.

[214] Patterson and Josling, "Regulating Biotechnology: Comparing EU and US Approaches," 7.

[215] Trump, "Synthetic Biology Regulation and Governance," 1142 (there is greater collaboration in the EU than in the US); C/f Patterson and Josling, "Regulating Biotechnology: Comparing EU and US Approaches," 7 (expressing the opposite view).

have valid objections to certain products based on health and other ethical grounds.[216]

Synthetic biology also undermines international biosafety regimes, particularly the Cartagena Protocol on Biosafety. Adopted in 2000 by 130 countries, excluding the US, this Protocol requires protective measures against Living Modified Organisms (LMOs), even without any scientific proof of risk. It defines LMO as *any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology*[217] and living organism means, *any biological entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids*.[218] Modern biotechnology is *the application of in vitro nucleic acid techniques, including rDNA and direct injection of nucleic acid into cells or organelles or* the *fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection*.[219] Put together, these definitions cover synthetic biology organisms.[220] Under that Protocol, the risks of LMOs are determined by comparing them with those of natural equivalents.[221] Synthetic biology, however, challenges this risk assessment method because organisms constructed from scratch with synthesised DNA lack natural comparators.[222] Those with expanded nucleotides or XNA, instead of DNA, pose greater risk assessment challenges.

To ensure biosafety, the Protocol requires consent from importing states before LMOs are transferred, but this applies only to physical biological material.[223] Synthetic biology circumvents this requirement since it relies mainly on digital genetic sequences, rather than tangible biological molecules. Digital sequences can discretely be imported

[216] Zainol et al., "Mandatory Labelling of Genetically Modified (GM) Foods," 208.
[217] Article 3(g).
[218] Article 3(h).
[219] Article 3(i)(a)(b)
[220] ICSWGSB, *A Submission to the SBSTTA,* 24.
[221] Annex III(5).
[222] Norton, "Synthetic Biology: Some Concerns of a Biodiversity Advocate," 2.
[223] ICSWGSB, *A Submission to the SBSTTA,* 24-25.

into a country and assembled into living systems, without triggering the advance consent requirement.[224]

In any case, since the Protocol applies to living organisms, transfer of sequences is excluded as these are not living organisms.[225] Moreover, consent from importing states is unnecessary, where LMOs are intended for contained use.[226] However, containment for GE-derived LMOs may be circumvented by synthetic biology organisms, given their intricate and fickle nature.[227] Lastly, non-participation of the US, leader in synthetic biology research, further undermines the Protocol.

CONCLUSION

Synthetic biology promises numerous benefits, but also poses biosafety challenges. Accessibility of synthetic biology to amateurs, open innovation ethos and affordable gene synthesis services further undermine biosafety measures. Moreover, self-governance, through biological measures, is challenging and vulnerable. Hence, the current regulatory frameworks and private measures are inadequate considering the challenges brought by the use of synthetic biology.

A more effective governance system combining self-governance and government regulation is thus advocated. Despite its shortcomings, self-governance offers flexibility to cope with the rapid pace of synthetic biology and facilitates collaboration to deal with its crossborderness. Therefore, inputs from scientists, DIYbio groups, industry, NGOs, citizens, local communities and funding bodies should inform policy and research lines.

Simultaneously, government regulation is vital to ensure greater transparency, provide effective enforcement mechanisms and strengthen public confidence in synthetic biology. Therefore, the current legal frameworks should be adapted to its novelties to ensure proper oversight over synthetic biologists and their research. Where necessary, entirely new laws should be enacted and adopted.

[224] Ibid.
[225] Ibid., 25.
[226] Article 6(2).
[227] ICSWGSB, *A Submission to the SBSTTA*, 25.

Regulatory agencies should be vested with adequate authority and their respective roles clarified to prevent jurisdictional gaps, overlap and confusion. Capacity enhancement, staff retraining and recruitment are also desirable. This will enable regulatory agencies to cope with the novelty, complexity, scale and diverse uses of future synthetic biology products. It will ensure quality and timely oversight compatible with innovation.

Risk research should be better funded to increase knowledge of the potential impacts of synthetic biology organisms, especially those without comparators. CRISPR editing and off-target gene effects also deserve attention. In respect of DIYbio groups, government oversight, coupled with outreach measures, is needed to manage biosafety risks associated with their experiments. Another focus area is emergency preparedness. As explained, physical containment of organisms is susceptible to natural disasters, accidents and sabotage, just as microbes can neutralise biological controls. Therefore, governments, non-profit human services agencies and funding bodies should collaborate to ensure systematic and effective service delivery during emergencies.

The crossborderness of synthetic biology also requires international coordination to ensure the uniformity and efficacy of governance measures. This will prevent legal and cultural diversities from influencing risk perception and creating inconsistent, lax regulatory standards that encourage regulatory shopping. The proposed governance system should evolve with synthetic biology to devise appropriate counter measures for emerging challenges. Synthetic biology governance should, however, reconcile risk mitigation and promotion of public confidence with the beneficial development of the technology. Therefore, regulation should neither be lax nor unduly stringent. It is hoped that other jurisdictions, especially in the developing world, will learn from the regulatory problems in the EU and the US discussed in this article. They provide a basis to develop or improve their own regulations to manage the risks of synthetic biology.