COMMENT

DR. FRANKENSTEIN, OR: HOW I LEARNED TO STOP WORRYING AND LOVE CRISPR-CAS9

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ABSTRACT: This comment examines the newly developed CRISPR-Cas9 genetic modification technology and discusses tentative steps towards new international regulations within which CRISPR-Cas9 users may operate. Researchers discovered that bacteria used CRISPR—clustered regularly interspaced short palindromic repeats—DNA sequences to encapsulate invasive phage DNA to defend themselves. While determining how bacteria used CRISPR DNA sequences to defend against invading phages, researchers discovered the CRISPR associated protein—Cas9—that efficiently cleaves DNA. One research team realized it could use the Cas9 protein to cleave DNA at any target in any organism. Since its development in 2013, genetic modification researchers around the world have adopted CRISPR-Cas9 as the premier genetic modification technology and are operating with no clear regulatory framework. This comment discusses how CRISPR-Cas9 democratizes genetic modification, provoking a new regulatory approach. I consider the current regulatory frameworks that could regulate CRISPR-Cas9's use, development, and commercialization. I then discuss the regulatory proposals for the similarly situated three-dimensional (3D) printing technology and nanotechnology and consider the potential pitfalls of applying these regulatory proposals to the CRISPR-Cas9 technology. I conclude the existing regulations that may capture CRISPR-Cas9 are unenforceable and that there is little willingness to create an internationally binding regulatory framework. I further conclude that private ordering may be an effective regulation strategy for this rapidly adopted and powerful new technology.

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The CRISPR-Cas9 genetic modification technology is a comparatively inexpensive,[1] widely available, and easy to use site-specific DNA cleaving—cutting—technology used to modify DNA.[2] Researchers discovered that bacteria used CRISPR—clustered regularly interspaced short palindromic repeats[3]—DNA sequences to encapsulate invasive phage DNA to defend themselves. While determining how bacteria used CRISPR DNA sequences to defend against invading phages, researchers discovered the CRISPR associated protein[4]—Cas9—that the bacteria use to cleave—cut—DNA. One research team realized it could use the Cas9 protein to cleave DNA at any target in any organism.[5] The Cas9 protein uses a single-sided section of the double-sided DNA—RNA—as a guide to detect the DNA-sequence location where it cleaves the DNA.[6] Researchers determined they could easily modify any DNA sequence by substituting their own guide RNA (gRNA) for the naturally occurring gRNA, directing the Cas9 protein to cleave DNA at a chosen point.[7]

The CRISPR-Cas9 technology represents a paradigm shift in genetic modification. First, unlike other genetic modification technologies, the CRISPR-Cas9 genetic modification technology works in any DNA-based organism with simple and inexpensive alterations.[8] Second, the CRISPR-Cas9 technology is both inexpensive and easy to use, requiring far less technical knowledge to operate. Simply put, CRISPR-Cas9 opens up the possibility for academic and scientific as well as less sophisticated home users.

In Part I of this comment, I discuss the CRISPR-Cas9 genetic modification technology's development and rapid evolution. In Part II, I discuss the application of CRISPR-Cas9 to bioengineering, including both the risks and benefits of bioengineering and the CRISPR-Cas9 technology. Part III addresses the existing national and international agencies and frameworks that currently regulate, or may regulate the use of the technology. In Part IV, I turn to my recommendations for the global regulatory framework that is best suited to the CRISPR-Cas9 genetic modification technology.

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1. An indiegogo.com crowd-funding campaign promises a CRISPR-Cas9 modification kit with instructions for a "donation" of $130. For a donation of $5,000, a donor will receive the kit with the necessary materials and instructions for the donor to develop their own genetically modified organism. Josiah Zayner, *DIY CRISPR Kits, Learn Modern Science by Doing*, INDIEGOGO, https://www.indiegogo.com/projects/diy-crispr-kits-learn-modern-science-by-doing [https://perma.cc/4ZJN-ZV54] (last visited Aug. 16, 2016); *see also* Kari Paul, *What Happens If Someone Uses This DIY Gene Hacking Kit to Make Mutant Bacteria?*, MOTHERBOARD (Dec. 7, 2015, 5:09 PM), http://motherboard.vice.com/read/what-happens-if-someone-uses-this-diy-gene-hacking-kit-to-make-mutant-bacteria.

2. Lei S. Qi et al., *Repurposing CRISPR as an RNA-Guided Platform for Sequence-Specific Control of Gene Expression*, 152 CELL 1173, 1173 (2013).

3. Elizabeth E. Pennisi, *The CRISPR Craze*, 341 SCIENCE 833, 834 (2013).

4. *Id.*; s*ee also* Wenyan Jiang et al., *CRISPR-Assisted Editing of Bacterial Genomes*, 31 NATURE BIOTECHNOLOGY 233, 233 (2013).

5. *See* Martin Jinek et al., *A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 SCIENCE 816, 820 (2012).

6. Pennisi, *supra* note 3, at 834.

7. *Id.* at 833–34.

8. Heidi Ledford, *CRISPR, the Disruptor*, 522 NATURE 20, 20 (2015).

CRISPR-Cas9 is a relatively cheap, widely available, and easy to use genetic modification technology, whose potential benefits outweigh its risks. Therefore, I argue that any regulatory framework should be flexible, emphasizing private ordering to legislative or governmental law-based regulation.

I. BACKGROUND OF CRISPR-CAS9 GENE MODIFICATION TECHNOLOGY

A. The Science

CRISPR were first identified in 1984 while genetic researchers were studying bacterial genes.[9] CRISPR are short sequences of DNA followed by the same sequence in reverse—the palindromic sequence—followed by "spacer" DNA—30 or so base pairs (BP) of DNA—which is followed by a repeat of the palindromic sequence.[10] Researchers have found these sequences in a significant proportion of bacteria and almost all archaea.[11] Many assumed these sequences were junk DNA.[12] However, because of the massive increase in available genetic information between 1987 and 2005, the junk theory was invalidated.[13]

In 2005, multiple research groups determined that the spacer DNA sequences matched the DNA sequences of phages ("viruses"), indicating that the spacer DNA may aid in microbial immunity.[14] Based on these findings, researchers suggested that bacteria and archaea may integrate phage DNA into their own DNA to identify and disable invasive DNA.[15] In 2007, researchers at Danisco[16] discovered that bacteria became more resistant to a phage by replacing the spacer DNA in the bacteria with DNA of a specific phage.[17]

A University of California, Berkeley research team, led by biochemist Jennifer A. Doudna,[18] discovered how the bacteria and archaea used the CRISPR-

9. Michael J. Stern et al., *Repetitive Extragenic Palindromic Sequences: A Major Component of the Bacterial Genome*, 37 CELL 1015, 1015 (1984). When discovered, researchers widely assumed that these sequences were junk DNA. Pennisi, *supra* note 3, at 834.

10. Pennisi, *supra* note 3, at 834.

11. *Id.* Archaea are organisms whose cells share characteristics of bacterial and eukaryotic cells—plant, animal, and fungi cells—but also differ from bacterial and eukaryotic cells. JOANNE M. WILLEY ET AL., PRESCOTT'S MICROBIOLOGY 473 (8th ed. 2011).

12. Pennisi, *supra* note 3, at 834.

13. Carl Zimmer, *Breakthrough DNA Editor Born of Bacteria*, QUANTA MAG. (Feb. 6, 2015), https://www.quantamagazine.org/20150206-CRISPR-dna-editor-bacteria.

14. *Id.*

15. *Id.*

16. Danisco was "a global enzyme and specialty food ingredients company" that DuPont bought in 2011. *DuPont to Acquire Danisco for $6.3 Billion*, THESTREET (Jan. 9, 2011, 9:57 PM), https://www.thestreet.com/story/10967518/1/dupont-to-acquire-danisco-for-63-billion.html; Chris V. Nicholson, *DuPont Offer for Danisco Succeeds*, N.Y. TIMES (May 16, 2011, 7:56 AM), http://dealbook.nytimes.com/2011/05/16/dupont-offer-for-danisco-succeeds.

17. Pennisi, *supra* note 3, at 834.

18. *Faculty: Jennifer A. Doudna*, U. CALIF. BERKELEY, http://chemistry.berkeley.edu/faculty/chem/doudna [https://perma.cc/GMZ9-P95C] (last visited Oct. 14, 2016); *Lab Members*, DOUDNA LAB, http://rna.berkeley.edu/people.html [https://perma.cc/J6WE-BSNM] (last visited Oct. 14, 2016). Dr. Jennifer A. Doudna is a professor of molecular and cell biology, and chemistry at the University

spacer DNA (crDNA) as a defense.[19] The team found that the microbes used a CRISPR-associated protein, Cas9,[20] guided by a single-sided section of crDNA—crRNA—to identify an invading phage.[21] Once identified, the Cas9 protein cleaves the phage DNA at the end of the crRNA complementary sequence, silencing the phage.[22]

The cell must process the phage DNA to use the Cas9 protein. The cell transcribes the CRISPR-spacer DNA into a long RNA molecule and then cleaves the long RNA into small spacer-derived crRNA.[23] The cell incorporates this crRNA as a guide RNA into the Cas9 protein nuclease through the help of a second strand of RNA, transactivating crRNA (tracrRNA).[24] The tracrRNA recruits the Cas9 protein.[25] The Cas9 protein identifies an invading phage when it finds a complementary DNA sequence to its "guide" crRNA.[26] Once identified, the Cas9 protein cleaves the DNA of the invading phage, silencing—disabling—it.[27]

Once researchers understood how bacteria and archaea used CRISPR as a defense system, they realized the process could be applicable as a genetic modification tool.[28] Doudna's team then modified the tracrRNA to include the crRNA as a single guide RNA (sgRNA) that could include any RNA sequence to guide the Cas9 protein to cut DNA at any point.[29] Thousands of researchers worldwide[30] are using the CRISPR-Cas9 genetic modification system daily to

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of Californian, Berkeley and a biochemical and structural biological researcher at the Howard Hughes Medical Institute. Doudna's research has focused on understanding the function of nonprotein RNAs. Doudna and her research team developed the CRISPR-Cas9 gene editing technology. *See generally* Dipali G. Sashital et al., *Mechanism of Foreign DNA Selection in a Bacterial Adaptive Immune System*, 46 MOLECULAR CELL 606 (2012).

19. *See generally* Sashital et al., *supra* note 18.

20. Type II CRISPR systems use a single multifunctional protein for both DNA identification and cleavage purposes. Cas9 is particularly useful because it is capable of producing double-stranded DNA breaks, whereas other Cas proteins are only capable of making single-stranded breaks. Cas9 is the CRISPR associated Protein in Type II systems and is the critical element in the simplicity and usefulness of the CRISPR-Cas9 technology. Jennifer A. Doudna & Emmanuelle Charpentier, *The New Frontier of Genome Engineering with CRISPR-Cas9*, 346 SCIENCE 1258096-1, 1258096-2–1258096-3, 1258096-5 fig. 4 (2014).

21. Jinek et al., *supra* note 5, at 816.

22. Doudna & Charpentier, *supra* note 20, at 1258096-2.

23. Jinek et al., *supra* note 5, at 816.

24. *Id.*

25. *Id.*

26. Pennisi, *supra* note 3, at 834.

27. *Id.*

28. Jinek et al., *supra* note 5, at 820; Doudna & Charpentier, *supra* note 20, at 1258096-1–1258096-4.

29. *Id.* at 819–20.

30. *Project Spotlight: CRISPR*, BROAD INST., https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/CRISPR ("The Zhang lab has trained thousands of researchers in the use of CRISPR-Cas9 genome editing technology . . . ."); *see also* Ann M. Taylor, *Genome Editing Writ Large: Rapid Adoption of CRISPR/Cas9 Technology Is Changing Our Ability to Explore Genomics and Treat Genetic Diseases*, CHEMICAL & ENGINEERING NEWS, Sept. 7, 2015, at 14, 16, http://cen.acs.org/articles/93/i35/Genome-Editing-Writ-Large.html ("[The] [b]est proof of all is the . . . thousands of labs around the world that use CRISPR every single day.").

modify "human cells, mice, rats, zebrafish, bacteria, fruit flies, yeast, nematodes, and crops, demonstrating broad utility for the technique."[31] CRISPR-Cas9 is a breakthrough because it uses an RNA based recognition of DNA rather than protein based recognition; a more effective and significantly easier process than producing a unique protein for every desired genetic cleavage.[32]

B. The Equipment

Understanding the equipment is essential to the possibility of developing any effective form of regulation. The equipment is important in this discussion because CRISPR-Cas9's final product can range from human immunodeficiency virus (HIV) curing pharmaceuticals to toxic-substance-eating bacteria, unlike numerous technologies whose final product will be a variation of the same object.[33] The CRISPR-Cas9 technology is not comprised of a specific set of parts assembled as one identifiable machine.[34] Thus, where regulation of the equipment itself may be useful in other proprietary or single-machine technologies, it is arguable that developing a framework to regulate the CRISPR-Cas9 equipment is ineffectively complicated, even if possible.

C. Patent Litigation

The CRISPR-Cas9 technology is currently the subject of a litigated patent dispute. While details of U.S. patent law are outside the scope of this article, a short discussion of the legal issues regarding ownership is worth a brief discussion.

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31. Pennisi, *supra* note 3, at 833–34.

32. Pennisi, *supra* note 3, at 835 ("The CRISPR system's "guide RNAs" are much easier to make than proteins, Barrangou says. 'Within a couple weeks you can generate very tangible results that using alternative methods would take months.'").

33. Consider traditional printers, industrial presses, plastic molding machines, and sewing machines. These can all be modified, but the end products will still be ink on some medium, a shaped piece of material, a plastic piece or item, and some material that is sewn to some other material. *See, e.g.*, Hirotaka Ebina et al., *Harnessing the CRISPR/Cas9 System to Disrupt Latent HIV-1 Provirus*, 3 SCI. REP., Aug. 26, 2013, at 1, 1, http://www.nature.com/articles/srep02510; Oscar N. Ruiz et al., *Characterization of Mercury Bioremediation by Transgenic Bacteria Expressing Metallothionein and Polyphosphate Kinase*, BMC BIOTECHNOLOGY, Aug. 12, 2011, at 1, 1, http://bmcbiotechnol.biomedcentral.com/articles/10.1186/1472-6750-11-82 (select "Download PDF" on right side of page) [https://perma.cc/AE4X-WLWF].).

34. The CRISPR-Cas9 system includes such nonproprietary equipment as "Filtered sterile pipette tips (Corning)," "Standard microcentrifuge tubes, 1.5 ml (Eppendorf, cat. no. 0030 125.150)," "Axygen PCR plates, 96 well (VWR, cat. no. PCR-96M2-HSC)," "Axygen 8-Strip PCR tubes (Fischer Scientific, cat. no. 14-222-250)," "Falcon tubes, polypropylene, 15 ml (BD Falcon, cat. no. 352097)," and "Falcon tubes, polypropylene, 50 ml (BD Falcon, cat. no. 352070)." None of the CRISPR-Cas9 system equipment is proprietary. F. Ann Ran et al., *Genome Engineering Using the* CRISPR-*Cas9 System*, 8 NATURE PROTOCOLS 2281, 2288–89 (2013), http://www.nature.com/nprot/journal/v8/n11/pdf/nprot.2013.143.pdf [https://perma.cc/XY6V-HGT2].).

1. *The Parties*

The parties to the patent litigation are Jennifer Doudna's research team and Feng Zhang's research team.[35] Doudna's team was the first to realize the potential use of the CRISPR-Cas9 technology for genetic modification.[36] However, Feng Zhang's team was the first to file a patent with the United States Patent and Trademark Office (USPTO) for the CRISPR-Cas9 technology's use in eukaryotic cells, specifically.[37]

2. *The Arguments and Legal Theory*

Under the Leahy-Smith America Invents Act (AIA), the rule governing patent priority converted from a "first-to-invent" to a "first-inventor-to-file" rule on March 16, 2013.[38] The first-to-invent rule gave priority to the party that could prove they were the first to "reduce to practice" the patented technology.[39] Doudna's and Zhang's teams each filed provisional patents with the USPTO on May 25, 2012, and December 12, 2012, respectively. Then, Doudna's and Zhang's teams filed final, nonprovisional patents on March 15, 2013, and October 15, 2013, respectively.[40] This means the patent priority will be assessed under the old first-to-invent rule. While Doudna's team was the first to file for patent rights, "Zhang requested prioritized examination under the USPTO's Track One program" leading to his patent issuing first.[41]

Doudna's team is currently challenging Zhang's patent rights with the USPTO, arguing that they were the first-to-invent.[42] Zhang argues that Doudna's early filings only applied to use in bacteria and not in eukaryotic cells, and is inapplicable to the uses his team patented.[43] Doudna's team initiated an interference proceeding to provide prior art that anticipates, or renders obvious, one or more of the claims in Zhang's application.[44] While the legal implications of the patent process are of little concern for the purposes of this comment, the outcome of this proceeding may be of importance going forward.

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35. Jennifer Doudna's research team is split between the University of California, Berkeley and the Helmholtz Center for Infection Research in Germany. Feng Zhang's team is split between the Broad Institute and MIT, both in Boston, Massachusetts. Mark Summerfield, *CRISPR—Will This Be the Last Great US Patent Interference?*, PATENTOLOGY (July 11, 2015, 8:08 PM), http://blog.patentology.com.au/2015/07/crispr-will-this-be-last-great-us.html [https://perma.cc/Y5FP-G4AT].

36. *Id.*

37. *Id.*

38. *Id.*

39. *Id.*

40. *Id.*

41. *Id.*

42. Heidi Ledford, *Bitter Fight over CRISPR Patent Heats Up*, 529 NATURE 265, 265 (2016).

43. Summerfield, *supra* note 35.

44. *Id.*; *See generally* 35 U.S.C. § 135 (2012) (providing the statutory requirements of a patent interference under the first-to-invent patent rule).

3. *Patent Holder's Licensing and Other Privileges*

The patent holders are important because they may withhold licensing the technology for any reason.[45] The caveat being that licensing is only effective in countries that respect these patent rights and provide a remedy should the license be violated or ignored. The owner of the CRISPR-Cas9 patent may deny licensing the technology for uses with which they disagree. This licensing right would have little impact in countries such as China, South Africa, Indonesia, Brazil, and Russia, especially in medically important cases.[46]

A refusal to license the technology may slow advances in areas of research with which the patent owners disagree. However, it is not likely to completely bar the technology's use for the unlicensed purposes because U.S. patent rights have no effect in foreign countries.[47] A final note worth mentioning is that researchers have developed alternative versions of the technology that possibly renders this particular patent dispute moot.[48]

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45. A patent grants the inventor a property right. The right the patent confers is "the right to exclude others from making, using, offering for sale, or selling" the invention in the United States or "importing" the invention into the United States. The patent owner may license the invention to others. No one else may make, use, offer for sale, sell, or import the invention without the patentees permission. *General Information Concerning Patents*, USPTO.COM (Dec. 30, 2015, 10:15 AM), http://www.uspto.gov/patents-getting-started/general-information-concerning-patents.

46. *See, e.g.*, Kevin Outterson, *Fair Followers: Expanding Access to Generic Pharmaceuticals for Low- And Middle-Income Populations*, *in* POWER OF PILLS 164, 164 (Jillian Clare Cohen et al. eds., 2006) ("In these cases, governments and patients may resort to unlicensed generic drugs and compulsory licensing . . . . Médecins Sans Frontières (MSF) broke the law when it began offering anti-retroviralantiretroviral therapy (ART) in Khayelitsha Township in South Africa in 2001."); *A Cure for High Prices: The United States and the Drug Firms Have Been Worsted over Patents*, 359 ECONOMIST 34, 34 (2001) ("Merck, an American company, had agreed to cut sharply the price it charges Brazil for Efavirenz, an AIDS treatment, after Mr. Serra had threatened to break its patent. . . . The Americans accept that WTO rules let Brazil break patents if it faces a health emergency. What they dispute is a clause in Brazil's patent law that lets it break a patent if the owner fails to make the product there."); DENNIS C. BLAIR ET AL., NAT'L BUREAU OF ASIAN RESEARCH, THE IP COMMISSION REPORT: THE REPORT OF THE COMMISSION ON THE THEFT OF AMERICAN INTELLECTUAL PROPERTY 1–2 (2013), http://www.ipcommission.org/report/IP_Commission_Report_052213.pdf ("For a variety of historical reasons . . . as well as because of economic and commercial practices and official policies aimed to favor Chinese entities and spur economic growth and technological advancement, China is the world's largest source of IP theft.").

47. Dowagic Mfg. Co. v. Minnesota Moline Plow Co., 235 U.S. 641, 650 (1915) ("The right conferred by a patent under our law is confined to the United States and its territories . . . and infringement of this right cannot be predicated of acts wholly done in a foreign country."); *see also Protecting Intellectual Property Rights (IPR) Overseas*, U.S. PAT. OFF., https://www.uspto.gov/patents-getting-started/international-protection/protecting-intellectual-property-rights-ipr (Oct. 1, 2015, 4:35 PM).

48. Antonio Regalado, *CRISPR Patent Fight Now a Winner-Take-All Match: Lab Notebooks Could Determine Who Was First to Invent a Revolutionary Gene-Editing Technology*, MIT TECH. REV. (Apr. 15, 2015), http://www.technologyreview.com/news/536736/CRISPR-patent-fight-now-a-winner-take-all-match. Evidence suggests that CRISPR-Cas9 is only one of many CRISPR associated proteins with identification and cleaving capability that may be used for genetic modification. Ledford, *supra* note 42, at 265. For example, Zhang's research group has found Cpf1, another enzyme that could be used as an alternative to Cas9. Bernd Zetsche et al., *Cpf1 Is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System*, 163 CELL 759, 761–62 (2015).

D. Applying CRISPR-Cas9 to Bioengineering and Therapeutics

The CRISPR-Cas9 technology is far cheaper and far simpler than other genetic modification technologies.[49] Possibly even more advantageous is that the CRISPR-Cas9 technology is not species specific.[50] The same technology can genetically modify bacteria, viruses, plants, fungi, and animals.[51] CRISPR-Cas9 technology appears capable of modifying any DNA-based organism.[52] Simply put, CRISPR-Cas9 has the ability to modify every known organism.[53] The specialization required by other technologies[54] to genetically modify different organisms is not a barrier. Previously developed genetic modification technologies required laborious alterations to conduct the genetic modifications of different organisms.[55] CRISPR-Cas9, however, eliminates this need, as the same protein and system works in all organisms.[56] Another important advantage of

49. Pennisi, *supra* note 3, at 836 ("The cost of admission is low: Free software exists to design guide RNA to target any desired gene, and a repository called Addgene, based in Cambridge, offers academics the DNA to make their own CRISPR system for $65."). Zinc Fingers, another enzyme based genetic modification tool, cost $5,000 for the critical component, while the RNA guide for a CRISPR-Cas9 system, the CRISPR-Cas9 critical component, costs as little as $30. Ledford, *supra* note 8, at 21 ("Researchers often need to order only the RNA fragment; the other components can be bought off the shelf. Total cost: as little as $30. 'That effectively democratized the technology so that everyone is using it,' says Haber. 'It's a huge revolution.'"). TALEN, a third enzyme based genetic modification tool, is both difficult and time consuming. A.A. Nemudryi et al., *TALEN and CRISPR/Cas Genome Editing Systems: Tools of Discovery*, ACTA NATURAE, July–Sept. 2014, at 19, 25. While researchers have made reductions to the time required to synthesize TALENs, the cost and complexity remain. Jeffrey M. Perkel, *Genome Editing with CRISPRs, TALENs and ZFNs*, BIOCOMPARE (Aug. 27, 2013), http://www.biocompare.com/Editorial-Articles/144186-Genome-Editing-with-CRISPRs-TALENs-and-ZFNs/.

50. Pennisi, *supra* note 3, at 833–34.

51. *Id.*

52. Jeffry D. Sander & J. Keith Joung, *CRISPR-Cas Systems for Editing, Regulating and Targeting Genomes*, 32 NATURE BIOTECHNOLOGY 347, 348 (2014).

53. Though it is possible that a DNA-less organism exists, no DNA-less organism has been discovered. Akira Hiyoshi et al., *Does a DNA-less Cellular Organism Exist on Earth?*, 16 GENES TO CELLS 1146, 1152 (2011).

54. Both TALENs and Zinc Fingers require the synthesis of a DNA specific protein. Holly Williams, *CRISPR: A Tour De Force in Gene-Editing*, BERKELEY SCI. REV. (Jan. 20, 2014), http://berkeleysciencereview.com/CRISPR-a-tour-de-force-in-gene-editing.

55. *See, e.g.*, Khaoula Belhaj et al., *Plant Genome Editing Made Easy: Targeted Mutagenesis in Model and Crop Plants Using The CRISPR/Cas System*, PLANT METHODS, Oct. 11, 2013, at 1, 8, https://plantmethods.biomedcentral.com/articles/10.1186/1746-4811-9-39 (select "Download PDF" on right side of page) ("The major advantage of the CRISPR/Cas technology over ZFNs and TALENs is that the method does not require elaborate design and time-consuming assembly of individual DNA-binding proteins. In contrast, the CRISPR/Cas system is versatile and only requires a single Cas9 nuclease that can be programmed by engineering the sgRNA."); Jim Yeadon, *Pros and Cons of ZNFs, TALENs, and CRISPR/Cas*, THE JACKSON LABORATORY: JAX BLOG (Mar. 4, 2014), https://www.jax.org/news-and-insights/jax-blog/2014/march/pros-and-cons-of-znfs-talens-and-CRISPR-cas.

56. *See* Sander & Joung, *supra* note 52, at 349; Hongge Jia & Nian Wang, *Targeted Genome Editing of Sweet Orange Using Cas9/sgRNA*, PLOS ONE, Apr. 7, 2014, at 1–2, http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0093806 (select "Download PDF" on right side of page).

the CRISPR-Cas9 technology is its ability to seek and cleave multiple genes at once.[57]

1. *Bacteria*

Researchers worldwide have genetically modified bacteria using CRISPR-Cas9.[58] Genetic modification of bacteria is potentially advantageous for many purposes. Bacteria have been used to clean up mercury pollution[59] and to detect arsenic in drinking water.[60] Medical researchers have modified bacteria to produce human insulin,[61] clotting factors for hemophilia,[62] and human growth hormone,[63] among other uses.[64]

2. *Viruses*

Derived from the bacteria's phage defense mechanism, researchers have already shown CRISPR-Cas9's potential strength as a viral therapy.[65] A therapeutic as effective for viruses as antibiotics are for bacterial infections has yet to be discovered. CRISPR-Cas9 dramatically shifts the paradigm as a potential therapeutic technology that can cure or silence the effects of viral infections.[66] By early 2014, researchers had already used CRISPR-Cas9 to silence HIV in

57. Sander & Joung, *supra* note 52, at 349.

58. *See, e.g.*, Eira Choudhary et al., *Gene Silencing by CRISPR Interference in Mycobacteria*, NATURE COMM., Feb. 25, 2015, at 1, http://www.nature.com/articles/ncomms7267.pdf [https://perma.cc/MTY6-Q3AY]; Jiang et al., *supra* note 4, at 233; Blake Wiedenheft et al., *RNA-Guided Genetic Silencing Systems in Bacteria and Archaea*, 482 NATURE 331, 332 (2012).

59. Oscar N. Ruiz et al., *supra* note 33, at 1.

60. Katharine Sanderson, *New Portable Kit Detects Arsenic in Wells*, CHEMICAL & ENGINEERING NEWS (Feb. 24, 2012), http://cen.acs.org/articles/90/web/2012/02/New-Portable-Kit-Detects-Arsenic.html.

61. Rik Derynck et al., *Human Transforming Growth Factor-α: Precursor Structure and Expression in E. Coli*, 38 CELL 287, 291 (1984).

62. S. W. Pipe, *The Promise and Challenges of Bioengineered Recombinant Clotting Factors*, 3 J. THROMBOSIS & HAEMOSTASIS 1692, 1692 (2005).

63. *See generally* Harold M. Schmeck Jr., *Human Growth Hormone Made by Bacteria: Tests in Patients Next Step in Several Diseases*, N.Y. TIMES, Jan. 6, 1981, at C1, http://www.nytimes.com/1981/01/06/science/human-growth-hormone-made-by-bacteria-tests-in-patients-next-step-in.html.

64. *See, e.g.*, Kevin Bullis, *Genetically Modified Bacteria Produce 50 Percent More Fuel*, MIT TECH. REV. (Oct. 3, 2013), http://www.technologyreview.com/news/519791/genetically-modified-bacteria-produce-50-percent-more-fuel; *Genetically Engineered Bacteria Prevent Mosquitoes from Transmitting Malaria*, JOHNS HOPKINS BLOOMBERG SCH. PUB. HEALTH (July 16, 2012), http://www.jhsph.edu/news/news-releases/2012/jacobs-lorena-bacteria.html.

65. Martyn K. White et al., *The CRISPR/Cas9 Genome Editing Methodology as a Weapon Against Human Viruses*, 19 DISCOVERY MED. 255, 256–57 (2015).

66. *See* Ebina et al., *supra* note 33, at 1 (discussing how CRISPR-Cas9 can identify and cleave—cut—the integrated viral DNA from the hosts' DNA, destroying the virus' effects).

human cells.[67] Other CRISPR-Cas9 research shows promise in treating other persistent viruses like hepatitis and herpes.[68]

Two of greatest barriers to market ready therapeutics are a reliable delivery system and off-target cleaving. Researchers worldwide are working to develop effective delivery systems.[69] Others are modifying CRISPR-Cas9 systems; some are using other Cas proteins and use strategies, showing lower rates of off-target cleavage.[70] While some applications of CRISPR-Cas9 therapies may be available within three to five years, researchers are hopeful that clinical trials for HIV and other viral infections will begin within the next ten years.[71]

3. *Plants*

Researchers are using CRISPR-Cas9 to genetically modify plants.[72] The research shows CRISPR-Cas9 plant modification is more successful and efficient than previously developed methods, promising an increase in the rates and outcomes of plant modifications.[73] Agricultural researchers are also attempting to create crop disease cures and crops immune to numerous diseases using CRISPR-Cas9.[74]

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67. One team of researchers used CRISPR-Cas9 to remove the integrated HIV DNA from the host genome, eradicating the infection and preventing new infection. Wenhui Hu et al., *RNA-Directed Gene Editing Specifically Eradicates Latent and Prevents New HIV-1 Infection*, 111 PROC. NAT'L ACAD. SCI. U.S. 11461, 11461 (2014).

68. A research team used the Cas9 protein from Francissella Novicada to bind to the hepatitis C virus RNA inhibiting the virus. Aryn A. Price et al., *Cas9-Mediated Targeting of Viral RNA in Eukaryotic Cells*, 112 PROC. NAT'L ACAD. SCI. U.S. 6164, 6165–66 (2015); *see, e.g.*, Zhaohua Zhong, *CRISPR-Cas System: A Feasible Solution For Getting Rid Of Persistent Viral Infection?*, 3 AM. J. VIROLOGY, no. 1, 2014, at 6, 6–7 (explaining that researchers have shown CRISPR-Cas9 system can cleave viral DNAs in either the episomal or integrated form); Jianbin Wang & Stephen R. Quake, *RNA-Guided Endonuclease Provides a Therapeutic Strategy to Cure Latent Herpesviridae Infection*, 111 PROC. NAT'L ACAD. SCI. U.S. 13157 (2014). While researchers have shown potential of previously developed forms of genetic modification as therapies, CRISPR-Cas9 has the advantage of size. The Cas9 protein's smaller size allows it to fit into a wider array of delivery systems, such as lentiviruses. Sander & Joung, *supra* note 52, at 348 box1.

69. Florian Schmidt & Dirk Grimm, *CRISPR Genome Engineering and Viral Gene Delivery: A Case of Mutual Attraction*, 10 BIOTECHNOLOGY J. 258, 260–63 (2015) (explaining that four different types of viral delivery systems previously researched are also capable of delivering CRISPR-Cas9 derived therapeutics, further explaining that a viral delivery system is particularly beneficial when the therapy requires modification over multiple cell divisions).

70. Ed Davis, *CRISPR-Cas9 Specificity: Taming Off-Target Mutagenesis*, GENECOPOEIA 1, 3 (2014), http://www.genecopoeia.com/wp-content/uploads/2014/04/Technotes_Specificity.pdf; Zetsche et al., *supra* note 48, at 761–62.

71. Carina Storrs, *Could the DNA-Editing CRISPR Revolutionize Medicine?*, CNN.COM (Aug. 12, 2015, 12:22 PM), http://www.cnn.com/2015/08/12/health/genesis-engine-dna-CRISPR-editas.

72. Doudna & Charpentier, *supra* note 20, at 1258096-1.

73. *Id.*

74. *See* Belhaj et al., *supra* note 55, at 8.

4. *Animals (Including Humans)*

CRISPR-Cas9 can genetically modify animal and human cells[75] and shows promise as an *in vivo* method for mammalian genetic modification.[76] Research shows CRISPR-Cas9's efficacy as a method of genetically modifying animal and human germline cells.[77] Recently, geneticists at Harvard Medical School used CRISPR-Cas9 to genetically modify pigs, knocking out the porcine endogenous retrovirus. This modification potentially allows for pig to human organ transplants by significantly reducing the immune response pig cells provoke in humans.[78]

E. Benefits and Risks of Bioengineering

1. *Benefits of Bioengineering*

Previously developed bioengineering technologies have provided many benefits in medical research, agriculture, and environmental restoration.[79] CRISPR-Cas9 greatly expands on these benefits because it is relatively cheap, easy to use, and more widely applicable than previously developed bioengineering techniques.[80] HIV therapies finally appear to be within reach thanks to CRISPR-Cas9.[81] CRISPR-Cas9 also has the therapeutic advantage of lentivirus delivery because of its smaller size in comparison to other gene editing

75. *See, e.g.*, Le Cong et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339 SCIENCE 819, 823 (2013); Woong Y. Hwang et al., *Efficient Genome Editing in Zebrafish Using a CRISPR-Cas System*, 31 NATURE BIOTECHNOLOGY 227, 227 (2013).

76. Danilo Maddalo et al., *In Vivo Engineering of Oncogenic Chromosomal Rearrangements with the CRISPR/Cas9 System*, 516 NATURE 423, 427 (2014).

77. *See* Puping Liang et al., *CRISPR Cas9 Mediated Gene Editing in Human Tripronuclear Zygotes*, 6 PROTEIN CELL 363, 363–64 (2015).

78. Sara Reardon, *Gene-Editing Record Smashed in Pigs*, NATURE (Oct. 6, 2015), http://www.nature.com/news/gene-editing-record-smashed-in-pigs-1.18525 ("Geneticist George Church of Harvard Medical School in Boston, Massachusetts, announced that he and colleagues had used the CRISPR/Cas9 gene-editing technology to inactivate 62 porcine endogenous retroviruses (PERVs) in pig embryos. These viruses are embedded in all pigs' genomes and cannot be treated or neutralized. It is feared that they could cause disease in human transplant recipients. Church's group also modified more than 20 genes in a separate set of pig embryos, including genes that encode proteins that sit on the surface of pig cells and are known to trigger a human immune response or cause blood clotting.").

79. Bioengineering has been used to create model animals for cancer, obesity, heart disease, diabetes, arthritis, substance abuse, anxiety, aging, and Parkinson disease. *See, e.g.*, K. Hansen & C. Khanna, *Spontaneous and Genetically Engineered Animal Models: Use in Preclinical Cancer Drug Development*, 40 EUROPEAN J. CANCER 858, 858 (2004); Ruiz et al., *supra* note 33, at 82; Grant Wilson, *Minimizing Global Catastrophic and Existential Risks from Emerging Technologies Through International Law*, 31 VA. ENVTL. L.J. 307, 316–17 (2013); *Knockout Mice*, NAT'L HUM. GENOME RES. INST. (Aug. 27, 2015), http://www.genome.gov/12514551. The United Kingdom has approved one gene therapy to fight pancreatitis. Sabrina Richards, *Gene Therapy Arrives in Europe*, SCIENTIST (Nov. 6, 2012), http://www.the-scientist.com/?articles.view/articleNo/33166/title/Gene-Therapy-Arrives-in-Europe.

80. *See, e.g.*, Perkel, *supra* note 49.

81. Ebina et al., *supra* note 33, at 1.

methods.[82] This size difference is especially beneficial because many genetic-modification-based therapeutics that could be developed require a delivery system to be effective *in vivo* therapies.[83] Viral delivery systems appear to be the most likely; the most promising being the adeno-associated virus (AAV) because it is not known to cause disease in humans.[84]

2. *Risks of Bioengineering*

Scientific research can be intentionally or unintentionally, purposefully or accidentally dangerous. Not all dangerous research is catastrophically dangerous, posing a "global catastrophic risk" (GCR) or an "existential risk" (ER).[85] It is arguable that genetic modification research presents the potential for both GCRs and ERs because of the possibility of intentional or unintentional applications, and the purposeful or accidental creation of super viruses, antibiotic resistant bacteria, or a massive crop blight that may spread far beyond a laboratory, to name a few.[86]

One argument dismisses genetic modification danger by considering past examples of potentially catastrophic research. For example, despite the outcries regarding the risk of publishing the research that produced an airborne form of the highly fatal H5N1 avian flu,[87] there has been no weaponizing of the virus or reports of human contraction. While dangerous laboratory research of such viruses may be alarming and generate highly viewed news headlines,[88] there are no documented disasters caused by genetic modification.[89] However, this argument is weak because the past is not a perfect predictor of the future. A simple

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82. *Id.* at 4.

83. Schmidt & Grimm, *supra* note 69, at 260–63.

84. *CRISPR Clears Major Obstacle Impeding Its Therapeutic Use*, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS (Apr. 2, 2015), http://www.genengnews.com/gen-news-highlights/CRISPR-clears-major-obstacle-impeding-its-therapeutic-use/81251106.

85. Global catastrophic risks (GCRs) threaten global damage to humans, while existential risks (ERs) threaten human extinction or severely and permanently reducing human quality of life on earth. Wilson, *supra* note 79, at 309–10.

86. Biological weapons and species modifications leading to complete ecosystem alterations or collapse are examples of other proposed potential risks. *See* Ledford, *supra* note 8, at 22, 24; Amy Maxmen, *The Genesis Engine*, WIRED, Aug. 2015, at 56, 58.

87. Nell Greenfieldboyce, *Journal Publishes Details on Contagious Bird Flu Created in Lab*, NAT'L PUB. RADIO (June 21, 2012, 3:08 PM), http://www.npr.org/sections/health-shots/2012/06/21/155504336/journal-publishes-details-on-controversial-bird-flu-experiments.

88. Maggie Fox, *Scientist Makes Mutant, Infectious Flu Virus in Lab*, NBC NEWS (June 11, 2014, 6:32 PM), http://www.nbcnews.com/health/health-news/scientist-makes-mutant-infectious-flu-virus-lab-n128936.

89. There are numerous theories regarding the danger of genetically modified crops, and one theory regarding a genetically modified supplement. *See* Ari Levaux, *A Potential Danger of Genetic Modification*, ATLANTIC (Jan. 9, 2012), http://www.theatlantic.com/health/archive/2012/01/the-very-real-danger-of-genetically-modified-foods/251051; Caitlin Shetterly, *The Bad Seed: The Health Risks of Genetically Modified Corn*, ELLE MAG. (July 24, 2013), http://www.elle.com/beauty/health-fitness/advice/a12574/allergy-to-genetically-modified-corn; *The Showa Denko Tryptophan Disaster Reevaluated*, PHYSICIANS & SCIENTISTS FOR RESPONSIBLE APPLICATION SCI. & TECH., http://psrast.org/demsd.htm (last updated Nov. 19, 2014). None of these theories present a large, verifiable risk of genetically modified organisms.

risk calculation would suggest that even a minute probability of a GCR or ER may justify the most severe of regulation until there is near certainty of safe performance.[90]

A second argument acknowledges the intentional and unintentional, purposeful and accidental risks of manmade genetic modification, while also acknowledging all other potential sources of catastrophe. If human-modified organisms are assumed to be the only potential threat, then the sensible solution is to halt all such research. However, human tinkering represents only a small portion of legitimate GCR and ER risks.[91] There are five known mass-extinction events[92] and multiple mass-human-death events,[93] none of which have been a byproduct of human genetic modification.[94] Thus, this argument considers even seemingly innocuous activities such as planting seeds that could have naturally occurring mutations, or the breeding of animals, or the act of human procreation presenting the risk of mutant humans all possibly leading to a global catastrophe.[95] Nature presents millions of times more opportunities for mutation than human-conducted genetic modification can produce.[96] Manmade genetic

90. Learned Hand's famous B<PL duty of care formula exemplifies this counterargument. United States v. Carroll Towing Co., 159 F.2d 169, 173 (2d. Cir. 1947) (explaining that a duty of care arises if the burden of adequate precautions ("B") is less than the probability that an accident will occur ("P"), multiplied by the magnitude the resulting injury from that accident occurring ("L")).

91. Nathanael Johnson, *Dealing with the Rational Fear About GMOs and Global Catastrophe*, GRIST (Sept. 11, 2015), http://grist.org/food/dealing-with-the-rational-fear-about-gmos-and-global-catastrophe.

92. Pincelli Hull, *Life in the Aftermath of Mass Extinctions*, 25 CURRENT BIOLOGY R941, R943 box1 (2015) (providing information regarding five known extinctions often called the "big five").

93. *See* GEORGE CHRISTAKOS ET AL., INTERDISCIPLINARY PUBLIC HEALTH REASONING AND EPIDEMIC MODELLING: THE CASE OF BLACK DEATH 110–14 (2005) (explaining that during the European plague of the 1300s it was common for fifty percent of the people in crowded cities to die); Curtis W. Marean, *When the Sea Saved Humanity*, 303 SCI. AM. 54, 55, 57 (2010) (discussing that evidence suggests that the ice age beginning about 195,000 years ago killed off the animals and plants humans relied on for food, reducing the human population to hundreds of breeding individuals).

94. Johnson, *supra* note 91 ("Not only is it theoretically possible for natural, bottom-up tinkering to create global black-swan events, these events have already occurred. Some 2.5 billion years ago, nature created a new biological technology: It was a cellular device which converted sunlight into energy, but also produced a corrosive, highly flammable, and poisonous gas—oxygen. It thrived and spread and multiplied. The climate change resulting from all the oxygen produced triggered a mass extinction, which we now know this as the Great Oxygenation Event, or the Oxygen Holocaust. Then, there's 'the Great Dyin'—the black swan event that wiped out 90 percent of all Earth's species at the end of the Permian period. What caused it? The evolution of a new kind of microbe is a leading theory to explain this mass extinction.").

95. *Id.*

96. *Id.* ("Microbes in the soil and water are swapping genes between species and creating new organisms at a rate that would put a billion Monsantos to shame. . . . Every form of breeding creates a potential for ruin. In fact, every time we plant a seed, we create a non-zero chance of unleashing a monster. . . . Any time we deal with something that is self-replicating, and self-supporting, and self-spreading, we are in the realm of potential for a systemic black swan."); *see* Yoshihiro

modifications represent a tiny fraction of all GCR and ER risks. Thus, eliminating human genetic modification would not decrease legitimate risks.[97]

II. BIOENGINEERING AND INTERNATIONAL LAW

A. An International Issue

Bioengineering is an international issue. All organisms frequently travel across jurisdictional borders, whether intentionally or unintentionally. As such, the technology and its products have little, if any, respect for national borders. The concern of a lab created creature's exposure to the natural world wreaking havoc is not new.[98] The democratization of the CRISPR-Cas9 technology significantly increases this concern by dramatically increasing the possible points of failure in labs across the United States, Europe, and China, among other countries and continents.[99] For effective regulation, the international community should not only be considered—but must be involved. It is worth considering existing frameworks when developing a regulatory framework for a democratized genetic modification technology such as CRISPR-Cas9.

1. *Convention on Biological Diversity*

In 1992, the United Nations Environmental Programme's Intergovernmental Negotiating Committee drafted and opened for signature and ratification The Convention on Biological Diversity (CBD).[100] The CBD attempts to require parties to conserve biological diversity, sustainably use the components of biological diversity, and share the benefits arising from the use of genetic resources.[101] The CBD is intended to protect natural environments, resources, species, and ecosystems,[102] but is not specifically intended as a framework for regulating bioengineering.[103] However, Article 8 of the CBD includes language that indicates a regulatory requirement. It states that each "Party shall, as far as possible and as appropriate":

> (g) Establish or maintain means to regulate, manage or control the risks associated with the use and release of living modified organisms resulting from biotechnology which are likely to have adverse environmental impacts that

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Kawaoka, *H5N1: Flu Transmission Work Is Urgent*, 482 NATURE 155, 155 (2012) (urging the scientific community to pursue transmission studies of highly pathogenic viruses despite the perceived risks because mammalian transmissibility may emerge in nature).

97. Johnson, *supra* note 91.

98. *See generally* MARY SHELLEY, FRANKENSTEIN; OR, THE MODERN PROMETHEUS (Marilyn Butler ed., Oxford Univ. Press 2008) (1818).

99. *See Project Spotlight: CRISPR*, *supra* note 30.

100. Convention on Biological Diversity, June 5, 1992, 1760 U.N.T.S. 79, 79 [hereinafter CBD]; *History of the Convention*, CONVENTION BIOLOGICAL DIVERSITY, https://www.cbd.int/history/default.shtml (last visited Aug. 26, 2016). While there are 196 Parties bound by the provisions of the CBD, the United States is not a Party to the convention. *List of Parties*, CONVENTION BIOLOGICAL DIVERSITY, https://www.cbd.int/information/parties.shtml (last visited Aug. 26, 2016).

101. CBD, *supra* note 100, at art. 1.

102. *History of the Convention*, *supra* note 100.

103. Wilson, *supra* note 79, at 339–40.

> could affect the conservation and sustainable use of biological diversity, taking also into account the risks to human health . . . .[104]

The CBD does not fully define living modified organisms (LMOs). However, the Cartagena Protocol on Biosafety to the Convention on Biological Diversity, a supplementary agreement to the CBD, defines LMOs as "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology."[105] CRISPR-Cas9 modified organisms are LMOs because they are the result of biotechnology.

While the language of Article 8 may be interpreted as regulatory, there is no clarity about specific actions required of the Parties.[106] Failure to regulate all LMOs that could adversely affect biodiversity and human health may be a violation of this provision. The CBD leaves this determination to the discretion of the Parties.[107] Furthermore, the CBD renders any regulatory language ineffective because it does not include an enforcement mechanism.[108] Though CRISPR-Cas9 research may fall under the CBD, it fails to provide an effectual regulatory framework.[109]

2. *Cartagena Protocol on Biosafety*

In September 2003, the Cartagena Protocol on Biosafety (Cartagena Protocol) entered into force as a supplementary agreement to the CBD to further its prerogatives.[110] The Cartagena Protocol governs the "transfer, handling and use

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104. CBD, *supra* note 100, at art. 8.

105. Cartagena Protocol on Biosafety to the Convention on Biological Diversity, art. 3(g), Jan. 29, 2000, 2226 U.N.T.S. 208 [hereinafter Cartagena Protocol]; *see also* Vienna Convention on the Law of Treaties, art. 31(2)(b), May 23, 1969, 1155 U.N.T.S. 331331. Article 31(2)(b) states that a treaty shall be interpreted in light of "[a]ny instrument which was made by one or more parties in [connection] with the conclusion of the treaty and accepted by the other parties as an instrument related to the treaty," including the Cartagena Protocol—a protocol to the CBD—expanding on the CBD's biosafety provisions. *Id.*

106. Wilson, *supra* note 79, at 340 ("[T]he [CBD] provisions do not establish specific actions that Parties must take. For example, measures like laboratory safety requirements, training of individuals handling highly fatal bioengineered organisms, and laboratory monitoring requirements are all absent from the CBD.").

107. The CBD does not define regulate, manage, and control. *See generally*, CBD, *supra* note 100.

108. The CBD does include a cause of action in the instance of one Party destroying the biological diversity of another Party, but does not have enforcement measures to regulate a Party's destruction of biological diversity within its own state. Daniel T. Jenks, *The Convention on Biological Diversity—An Efficient Framework for the Preservation of Life on Earth?*, 15 NW. J. INT'L L. & BUS. 636, 656 (1995). Without an enforcement mechanism there is no penalty or cost for a party's failure to meet a target or to generally comply with the CBD, and the achievement of the goals has been limited. Wilson, *supra* note 79, at 340–41. By the end of 2014 only five of fifty-six outlined targets determined in a 2010 strategic plan were on course to be met by the 2020 goal. *Global Biodiversity Outlook 4—Summary and Conclusions*, SECRETARIAT OF THE CONVENTION ON BIOLOGICAL DIVERSITY 10–14 (2014), https://www.cbd.int/gbo/gbo4/gbo4-summary-en.pdf.

109. It is important to note that the United States is not one of the 196 countries that are Party to the CBD. *List of Parties*, *supra* note 100.

110. *About the Protocol*, CONVENTION ON BIOLOGICAL DIVERSITY, http://bch.cbd.int/protocol/background (last updated May 29, 2012). There are currently 170 Parties to the Cartagena

of living modified organisms" from one member state to another.[111] It includes a wider range of organisms than the CBD, with "sterile organisms, viruses and viroids" included in its definition of "living organisms."[112] While intended to govern the movements of LMOs across international borders, Article 4 has been interpreted to establish that the Cartagena Protocol applies to any use of LMOs.[113]

The Cartagena Protocol includes risk assessment and risk management requirements. Articles 15 and 16 include the language that is most applicable to the regulation of CRISPR-Cas9. Article 15 requires the undertaking of "risk assessments."[114] Specifically, Article 15 requires Parties to evaluate the likelihood and consequences of the adverse effects of an LMO, to estimate the "overall risk posed by the [LMO]," and to recommend whether the risks are acceptable or manageable. Article 15 then requires Parties to identify strategies to manage the identified risks.[115] Article 16 requires Parties to "regulate, manage, and control risks . . . associated with the use, handling and transboundary movement of living modified organisms."[116] Article 16 requires Parties to impose "measures . . . to the extent necessary to prevent adverse effects" of LMOs on biodiversity and human health as well as the "unintentional transboundary movements" of LMOs based on the conclusions of the risk assessment.[117]

Many policymakers and commentators have argued that the Cartagena Protocol's risk assessment and risk management requirements are largely ineffective.[118] The Cartagena Protocol gives decision makers wide discretion in assessing and determining LMO risk management.[119] In its third meeting, the Cartagena Protocol Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management explained that "risk assessors . . . provide recommendation(s) as to whether or not risks [arising from LMOs] are acceptable or manageable . . . in relation to [their nation's] protection goals."[120] Final approval

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Protocol. Similar to the CBD, the United States is not one of the Parties. *Parties to the Protocol and Signature and Ratification of the Supplementary Protocol*, CONVENTION ON BIOLOGICAL DIVERSITY, http://bch.cbd.int/protocol/parties (last updated June 11, 2014) [hereinafter *Parties to the Cartagena Protocol*].

111. Cartagena Protocol, *supra* note 105, at art. 1.

112. *Id.* at art. 3(h).

113. *Id.* at art. 4; *see also* RUTH MACKENZIE ET AL., AN EXPLANATORY GUIDE TO THE CARTAGENA PROTOCOL ON BIOSAFETY 54 (2003), http://www.unep.org/biosafety/files/IUCNGuide%20on%20the%20CPB.pdf ("[T]he term "use" would appear to refer to any operation involving LMOs.").

114. Cartagena Protocol, *supra* note 105, at art. 15.

115. *Id.* at art. 40, Annex III.

116. *Id.* at art. 16.

117. *Id.* at art. 16(2)–(3).

118. *See, e.g.*, Wilson, *supra* note 79, at 342; Katharine E. Kohm, Comment, *Shortcomings of the Cartagena Protocol: Resolving the Liability Loophole at an International Level*, 27 UCLA J. ENVTL. L. & POL'Y 145, 156–57 (2009).

119. Wilson, *supra* note 79, at 342.

120. *See* Rep. of the Third Meeting of the Ad Hoc Tech. Expert Grp. on Risk Assessment and Risk Management Under the Cartagena Protocol on Biosafety, at 18, U.N. Doc. UNEP/CBD/BS/AHTEG-RA&RM/3/4 (2011), http://www.cbd.int/doc/meetings/bs/bsrarm-03/official/bsrarm-03-04-en.pdf.

for the use of LMOs is reserved for "the decision maker to decide."[121] The final approval is "typically decided at a political level and may vary from country to country."[122] These determinations are left to the discretion of the individual Parties because there is no standardized definition of acceptable risks or management requirements.

The CBD's risk assessment and management discretion gives rise to a patchwork of regulatory policies. A good example of this patchwork is the wide variance in genetically modified (GM) crops between countries. The United States, Argentina, and Canada's GM crops represent 98% of the world's total GM crop by acreage, versus that of European countries and Japan.[123] While there is some value in each Party's ability to individually evaluate risks, the result is a worldwide patchwork of regulatory instruments rather than an internationally cohesive regulatory framework. The Cartagena Protocol has no ability to effectively set boundaries for CRIPSR-Cas9 use because each Party may choose its risk threshold[124]—circumstances commonly shown to create a regulatory "race to the bottom."[125]

The Cartagena Protocol is not an effective regulatory scheme because it fails to include any means of enforcement for its liability scheme.[126] Similar to

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121. *Id.*

122. *Id.*; *see* Guidance on Risk Assessment on Living Modified Organisms, Report of the Third Meeting of the Ad Hoc Technical Expert Group on Risk Assessment and Risk Management Under the Cartagena Protocol on Biosafety, at 18, U.N. Doc. UNEP/CBD/BS/AHTEG-RA&RM/3/4 (2011), http://www.cbd.int/doc/meetings/bs/bsrarm-03/official/bsrarm-03-04-en.pdf.

123. Wilson, *supra* note 79, at 343.

124. A few examples of differences in cultures leading to differing boundaries are cloning and embryonic stem cell research. During the early 2000s in China, there was no widespread ethical debate regarding cloning or embryonic stem cell research. There were no laws preventing government funded research, nor any serious proposals to ban such research. Conversely, in the United States, there were federal laws that prohibited some government funded embryonic stem cell research, and this was assumed to apply to cloning as well. The U.S. has removed most barriers, though some states still ban embryonic stem cell research and have cloning laws. *See* Karby Leggett & Antonio Regalado, *Fertile Ground: As West Mulls Ethics, China Forges Ahead in Stem-Cell Research*, WALL ST. J., Mar. 6, 2002, at A1; *Human Cloning Laws*, NAT'L CONFERENCE ST. LEGISLATURES, http://www.ncsl.org/research/health/human-cloning-laws.aspx (last updated Jan. 2008).

125. *See, e.g.*, SANFORD F. SCHRAM, AFTER WELFARE: THE CULTURE OF POSTINDUSTRIAL SOCIAL POLICY 91 (2000); William L. Cary, *Federalism and Corporate Law: Reflections upon Delaware*, 83 YALE L.J. 663 (1974) (discussing how the patchwork of corporation laws throughout the United States incentivized states to create the least restrictive corporation laws to retain and increase incorporation within each state to enjoy the economic benefits, leaving substantive regulation of corporations to the federal government). The race to the bottom is evidenced in current biotechnology regulation as nations show no interest in imposing any regulations that may slow the biotech advancements within their nation. This is largely a function of its economic benefits. Kenneth W. Abbott et al., *Transnational Regulation of Nanotechnology: Reality or Romanticism*, *in* INTERNATIONAL HANDBOOK ON REGULATING NANOTECHNOLOGIES 525, 525 (Graeme A. Hodge et al. eds., 2010).

126. The Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety creates a liability scheme for transboundary damage from LMOs that includes unintentional transboundary movements. *See* Conference of the Parties to the Convention on Biological Diversity [CBD], *Report of the Fifth Meeting of the Conference of the Parties to the Convention on Biological Diversity Serving as the Meeting of the Parties to the Cartagena Protocol*

the CBD, the Cartagena Protocol fails to include any meaningful recourse should a Party violate the agreement.[127] Being the technology's birthplace with some of the most sophisticated labs; it is also worth noting that the United States is a Party to neither the CBD nor the Cartagena Protocol.[128] This significantly limits the CBD's and Cartagena Protocol's CRISPR-Cas9 regulatory impact. Further weakening its CRISPR-Cas9 regulatory value, the Cartagena Protocol does not address the ethical questions that do not pose an assessed threat to either biodiversity or human life, leaving open the ethically important "should we" dilemma.

3. *Biological Weapons Convention*

The Biological Weapons Convention (BWC) entered into force on March 26, 1975 with the overarching objective of preventing biological warfare within and between nation states.[129] The BWC prohibits Parties from developing, producing, stockpiling, acquiring, or retaining "microbial or other biological agents [or] toxins . . . that have no justification for prophylactic, protective or other peaceful purposes . . . ."[130] For the 155 Parties, including the United States, Russia, China, and India,[131] the BWC does not limit or regulate any legitimate research being conducted for prophylactic, protective, or other peaceful purposes.[132] Thus, research conducted for peaceful purposes, whose results may be particularly dangerous, would not fall under the BWC.

The BWC obligates Parties to restrict transfers of biological weapon information or technology, except for peaceful purposes.[133] Article III of the BWC states that a Party cannot "transfer, . . . directly or indirectly . . . assist, encourage, or induce any State, group of States or international organization to manufacture or otherwise acquire any of the agents, toxins, weapons, equipment or

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on Biosafety, arts. 2–5, UN Doc. UNEP/CBD/BS/COPMOPCOP-MOP/5/17, annex (Oct. 15, 2010), http://bch.cbd.int/protocol/NKL_text.shtml. However, while this allows for redress in the event of harm, it is not additionally regulating usage outside of the existing patchwork of state-based regulations. Even if its liability scheme were considered regulatory, it is currently not in force, not yet having achieved the forty signatures necessary. *Parties to the Protocol and Signature and Ratification of the Supplementary Protocol*, CONVENTION ON BIOLOGICAL DIVERSITY (June 11, 2014), http://bch.cbd.int/protocol/parties/#tab=1.

127. Cartagena Protocol, *supra* note 105, at art. 16.

128. The United States cannot be a Party to the Cartagena Protocol because it is not a Party to the CBD. *Frequently Asked Questions on the Cartagena Protocol on Biosafety (CPB)*, U.S. DEP'T ST. ARCHIVE, http://2001-2009.state.gov/g/oes/rls/or/2004/29751.htm (last updated Jan. 20, 2009). Other notably missing countries include Canada, Australia, and Russia. *See Parties to the Cartagena Protocol*, *supra* note 110.

129. Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction, art. I, Apr. 10, 1972, 26 U.S.T. 583, 1015 U.N.T.S. 163, 163, 166 [hereinafter BWC].

130. *Id.*

131. *Membership of the Biological Weapons Convention*, THE UNITED NATIONS OFFICE AT GENEVA, http://www.unog.ch/__80256ee600585943.nsf/(httpPages)/7be6cbbea0477b52c12571860035fd5c (last visited Feb. 5, 2016).

132. *See* BWC, *supra* note 129, at art. I.

133. *Id.* at art. X(2).

means of delivery specified in Article I . . . ."[134] Parties are required to ensure that transfers of their biotechnologies do not violate this provision. However, Article X exempts "exchange of equipment, materials, and scientific and technological information" developed to prevent disease or for other peaceful purposes.[135] A Party would have to actively seek to exchange technology for biological weapons use to violate the BWC.

Multiple issues arise when applying the BWC to CRISPR-Cas9 technology. First, even the most nefarious uses of bioengineering can be conducted under the guise of a peaceful purpose. Despite the danger it may present, almost all genetic modification research may be characterized as prophylactic, protective, or otherwise peaceful in purpose.[136] Secondly, the BWC does not apply to the peacefully intended but ethically questionable uses of CRISPR-Cas9. Thirdly, the BWC is nonbinding, and there is no compliance-monitoring body or enforcement mechanism.[137] While the BWC attempts to address the weaponry aspect of bioengineering, it fails to effectively do so. Provisions are easily circumvented, and there is no enforcement body or mechanisms. Thus, the BWC is an ineffective instrument to regulate the CRISPR-Cas9 technology.

B. Self-Regulation: Asilomar Conference on Recombinant DNA

In the early 1970s, recombinant DNA technology was stirring up controversy.[138] Fears of super virus, antibiotic resistant bacteria, toxin-producing microbe, and cancer-causing agent creation weighed on the scientific community.[139] International researchers gathered at a nucleic acid conference[140] and called for a voluntary moratorium on certain recombinant DNA research until a conference to evaluate the state and risks of the new technology was held.[141] Researchers universally observed the moratorium.[142] In 1975, the *Asilomar Conference on Recombinant DNA* (Asilomar) produced research guidelines promulgated by the National Institutes of Health and similar agencies in other countries.[143] Asilomar focused largely on public health and safety, and research

134. *Id.* at art. III.

135. *Id.* at art. X(1).

136. *See* Fox, *supra* note 88.

137. Wilson, *supra* note 79, at 345; Martin Matishak, *BWC Review Conference Could Revive Verification Debate, Chairman Says*, NUCLEAR THREAT INITIATIVE: GLOBAL SEC. NEWSWIRE (Jul. 8, 2011), http://www.nti.org/gsn/article/bwc-review-conference-could-revive-verification-debate-chairman-says/.

138. Paul Berg & Maxine F. Singer, *The Recombinant DNA Controversy: Twenty Years Later*, 92 PROC. NAT'L ACAD. SCI. U.S.A. 9011, 9011 (1995).

139. *Id.*

140. Donald S. Fredrickson, *Asilomar and Recombinant DNA: The End of the Beginning, in* INST. OF MED. COMM. TO STUDY DECISION MAKING, BIOMEDICAL POLITICS 258, 270–71 (Kathi E. Hanna ed., 1991), http://www.ncbi.nlm.nih.gov/books/NBK234217.

141. Berg & Singer, *supra* note 138, at 9011.

142. *Id.*

143. Some of the other countries include the United Kingdom, Russia, and France. Fredrickson, *supra* note 140, at 274, 282, 284 n.1.

ethics.[144] The conference succeeded in achieving its goal of instituting a moratorium and developing and promulgating guidelines that the research community followed.[145]

Asilomar's success may be instructive. The main guidelines focused on safe research procedure. Recommendations included biological barriers such as bacterial hosts that could not survive in the natural environment.[146] Participants developed research facility guidelines, and the classification of the research risks thereof.[147] Asilomar guidelines also prohibited certain research, including "the cloning of recombinant DNAs derived from highly pathogenic organisms . . . , DNA containing toxin genes, and large scale experiments . . . using recombinant DNAs that are able to make products potentially harmful to man, animals, or plants."[148] This research was banned because the risks presented could not be effectively contained by the currently available safety systems.[149]

Asilomar represents an ideal set of circumstances for consensus building. Recombinant DNA uncovered a world of genetic modification previously unknown at a time when researchers knew little about the genome.[150] The technologies required a more sophisticated body of knowledge and more time than CRISPR-Cas9.[151] Thus, the community of capable researchers was much smaller,[152] increasing the likelihood of consensus.

C. Human Dignity Instruments

There are numerous soft laws and legally binding regional agreements, but no international treaties or conventions regulating heritable human genetic modifications.

1. *Council of Europe's Convention on Human Rights and Biomedicine*

The foremost binding agreement that regulates human genetic engineering is the Council of Europe's Convention on Human Rights and Biomedicine

144. *Id.* at 277.

145. Berg & Singer, *supra* note 138, at 9011.

146. Paul Berg et al., *Summary Statement of the Asilomar Conference on Recombinant DNA Molecules*, 72 PROC. NAT'L ACAD. SCI. U.S.A. 1981, 1982 (1975).

147. *Id.* at 1982–83.

148. *Id.*

149. *Id.*

150. The human genome had not yet been sequenced, and would not be fully sequenced until 2003. National Institute of Health: National Human Genome Research Institute, *About NHGRI: A Brief History and Timeline*, GENOME.GOV, http://www.genome.gov/10001763 (last updated July 5, 2016).

151. *See* Maxmen, *supra* note 86, at 56; Mark Esposito, *New Biotechnology Puts Scientists on the Road to CRISPR Discoveries*, BREAKINGBIO, http://www.breakingbio.org/new-biotechnology-puts-scientists-on-the-road-to-crispr-discoveries/ (last visited Oct. 19, 2016).

152. Maxmen, *supra* note 86, at 64 ("Genome editing started with just a few big labs putting in lots of effort . . . . Now it's something that someone with a BS and a couple thousand dollars' worth of equipment can do." (quoting Hank Greely, Professor of Law and Director of the Center for Law and the Biosciences, Stanford University)).

(CHRB), which entered into force on December 1, 1999 with thirty-five Parties.[153] Article 13 states that "[a]n intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants."[154] Even if the modifications are not intended to modify the genome of descendants, the CHRB Explanatory Report explains that Article 13 prohibits inheritable genetic alterations of humans.[155] The CHRB does not regulate every use of CRISPR-Cas9, though it does regulate any human germline modifications.[156] In doing so, CHRB regulates one of the most prevalent ethical concerns regarding human genetic modification: eugenics.[157] Despite the CHRB's potential efficacy, only thirty-four out of forty-seven Council of Europe Member States are signatories. Additionally, there is no participation by non-European nations, severely limiting the CHRB's global effectiveness.[158]

2. *Rome Statute*

Some argue that heritable genetic modification (HGM) may constitute a "crime against humanity."[159] This argument has not garnered much support. However, if it were determined that HGM were a crime against humanity, it would violate the Rome Statute of the International Criminal Court (Rome Statute). The Rome Statute defines crimes against humanity as acts "committed as

153. *Chart of Signatures and Ratifications of Treaty 164*, COUNCIL EUR., http://www.coe.int/en/web/conventions/search-on-treaties/-/conventions/treaty/164/signatures (last visited Feb. 5, 2016).

154. Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine, art. 13, Apr. 4, 1997, CETS No. 164 [hereinafter CHRB].

155. *Explanatory Report to the Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*, COUNCIL EUR. 15 ¶ 91 (Dec. 17, 1996), https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=09000016800ccde5.

156. Germline cells are the cells that pass on genes from generation to generation through sexual reproduction. *Germline*, GENETICS HOMES REFERENCE: NATIONAL INSTITUTES OF HEALTH, (Feb. 8, 2016), https://www.ncbi.nlm.nih.gov/books/NBK5191/ (search under "G" for "germline").

157. *See* Heidi Ledford, *The Landscape for Human Genome Editing*, 526 NATURE 310 (2015).

158. *Signatories to the CHRB*, COUNCIL EUR., http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=164&CM=8&DF=01/04/2012&CL=ENG (last updated Feb. 23, 2016). Notably missing countries include Germany, Ireland, Russia, and the United Kingdom.

159. George J. Annas, Lori B. Andrews and Rosario M. Isasi, two law professors and a healthcare fellow, respectively, have argued that human cloning and inheritable genetic modification may have beneficial application in certain extreme circumstances, but may otherwise be crimes against humanity. George J. Annas et al., *Protecting the Endangered Human: Toward an International Treaty Prohibiting Cloning and Inheritable Alterations*, 28 AM. J.L. & MED. 151, 153 (2002). Annas, Andrews, and Isasi proceed to explain their view that human modifications, if successful, could lead to a whole new species of "posthumans" which would likely view "normal" humans as "inferior . . . and fit for slavery or slaughter." *Id.* at 161–62 (first citing George J. Annas, *The Man on the Moon, Immortality, and Other Millennial Myths: The Prospects and Perils of Human Genetic Engineering*, 49 EMORY L.J. 753, 776-80 (2000); then at 161–62 (citing FRANCIS FUKUYAMA, OUR POSTHUMAN FUTURE: CONSEQUENCES OF THE BIOTECHNOLOGY REVOLUTION (2002); and then citing Francis Fukuyama, *Natural Rights and Human History*, THE NAT'L INT., Summer 2001, at 19, 30 (2002)).

a part of a widespread or systemic attack directed against any civilian population, with knowledge of the attack."[160] "Attack" is defined as "a course of conduct involving multiple commissions of acts."[161] The plain language of the Rome Statute only includes acts that are attacks "directed against" a civilian population. Even if intended to create posthumans, the creators of HGM humans are not likely executing an "attack." Posthuman oppression of humans may be considered an attack, but not one perpetrated by those who created the posthumans. Thus, HGM does not likely violate the Rome Statute.

3. *UNESCO's Universal Declaration on Bioethics and Human Rights*

The Universal Declaration on Bioethics and Human Rights (UDHR) is intended "to deal with ethical issues raised by rapid changes in medicine, life sciences and technology."[162] The UDHR is a nonbinding framework[163] adopted in 2005 that applies to all United Nations Educational, Scientific, and Cultural Organization (UNESCO) Member States[164] "to guide States in the formulation of their legislation, policies or other instruments in the field of bioethics."[165] Article 3 requires that "[h]uman dignity, human rights and fundamental freedoms are to be fully respected . . . [with] the interests and welfare of the individual . . . hav[ing] priority over the sole interest of science or society."[166] While no provision directly mentions human genetic modification, Article 16 calls for regard to be given to "the impact of life sciences on future generations, including their genetic constitution."[167] Further, Article 19 suggests the establishment of "pluralist ethics committees . . . in order to . . . assess the relevant ethical, legal, scientific and social issues related to research projects involving human beings."[168] All of these provisions could be interpreted to regulate some CRISPR-Cas9 uses, though none are binding. In a 2014 study, researchers from Hokkaido

160. Rome Statute of the International Criminal Court art. 7, Jul. 17, 1998, 2187 U.N.T.S. 90.

161. *Id.*

162. Press Release, UNESCO, UNESCO Panel of Experts Calls for Ban on "Editing" of Human DNA to Avoid Unethical Tampering with Hereditary Traits, UNESCOPRESS (May 10, 2015), http://www.unesco.org/new/en/media-services/single-view/news/unesco_panel_of_experts_calls_ for_ban_on_editing_of_human_dna_to_avoid_unethical_tampering_with_hereditary_traits/#.Vi7mOH6rSUl.

163. Michael Kirby, *Human Rights and Bioethics: The Universal Declaration of Human Rights and UNESCO Universal Declaration of Bioethics and Human Rights*, 25 J. CONTEMP. HEALTH L. & POL'Y 309, 316 (2009).

164. Koïchiro Matsuura, *Foreword* to U.N. Educ. & Sci. Cultural Org., *Universal Declaration on Bioethics and Human Rights*, UNESCO DIVISION OF ETHICS OF SCI. & TECH. SOC. & HUM. SCI. SECTOR (2006), http://unesdoc.unesco.org/images/0014/001461/146180E.pdf. UNESCO currently includes 195 Member States and 10 Associate Member States. *Countries, United Nations Educational, Scientific and Cultural Organization*, UNESCO.INT, http://www.unesco.org/new/en/member-states/countries (last visited Aug. 28, 2016).

165. UNESCO, General Conference of UNESCO, *Universal Declaration on Bioethics and Human Rights*, art. 2, 33rd sess. U.N. Doc. A/CONF.183/9 (Oct. 19, 2005), http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html.

166. *Id.* at art. 3.

167. *Id.* at art. 16.

168. *Id.* at art. 19.

University reviewed thirty-nine countries, finding that twenty-five banned human germline editing, with four other countries having guidelines. Thus, while nonbinding, the UDHR may influence and provide countries guidance on their own public policy.

III. DEMOCRATIC TECHNOLOGY FRAMEWORK PROPOSALS

A. 3D Printing

Three-dimensional (3D) printing shares a similar regulatory space to CRISPR-Cas9 technology. Like CRISPR-Cas9, 3D printing democratizes manufacturing. 3D printing and the ability to manufacture all forms of "thing" at home is not a new concept.[169] However, the latest technology has greatly reduced the price and the sophistication required to do so.[170] Users still require some technical knowledge to design or prepare 3D printable object models, which may prevent 3D printers from becoming household items like cell phones and personal computers.[171] However, it is likely there will be many professional manufacturers, and a smaller group of "tinkerers" that will end up using the technology, further democratizing the manufacture of innumerable widgets. With democratization comes the questions of proper use, dangers, and appropriate regulation.

One proposal for a 3D printing regulatory framework reflects many of the same fears and issues associated with the CRISPR-Cas9 technology. In his article, Peter Jensen-Haxel[172] makes the point that because 3D technology may be widely available, regulation of the technology itself may be near impossible. However, Jensen-Haxel further explains that the raw materials needed to produce 3D manufactured items will likely have a central point of production, which could act as a "regulatory pressure point."[173]

Jensen-Haxel argues that the regulation of a material necessarily involves a determination of either harmful inherent properties or harmful emergent ex-

169. *See* C. Lee Ventola, *Medical Applications for 3D Printing: Current and Projected Uses*, 39 PHARMACY & THERAPEUTICS 704, 704 (2014).

170. *Id.* at 705.

171. Nick Allen, *Why 3D Printing Is Overhyped (I Should Know, I Do It for a Living)*, GIZMODO (May 17, 2013, 9:11 AM), http://gizmodo.com/why-3d-printing-is-overhyped-i-should-know-i-do-it-fo-508176750.

172. "Peter Jensen-Haxel is a patent attorney in the areas of additive manufacturing, blockchain technology, and cloud computing architecture," with a background in Biological Chemistry. Peter Jensen-Haxel, *A New Framework for a Novel Lattice: 3d Printers, DNA Fabricators, and the Perils in Regulating the Raw Materials of the Next Era of Revolution, Renaissance, and Research*, 5 WAKE FOREST J.L. & POL'Y 231, 231 n.* (2015) [hereinafter *A New Framework for a Novel Lattice*]; Peter Jensen-Haxel, Comment, *3D Printers, Obsolete Firearm Controls, and the Right to Build Self-Defense Weapons Under* Heller, 42 GOLDEN GATE L. REV. 447, 447 n.* (2012).

173. *A New Framework for a Novel Lattice*, *supra* note 172, at 263.

ternal properties, using dynamite and heroin as examples of each, respectively.[174] Dynamite is inherently dangerous and heroin has harmful emergent external properties in the form of negative societal effects when available to a population.[175] However, at least one of the components of heroin, acetic anhydride, has numerous other uses having nothing to do with illegal drugs.[176] Acetic anhydride is regulated despite these other uses. In short, while there are reasons to regulate dynamite, regulating materials that only become dangerous when combined with certain other materials may be worth regulating. Jensen-Haxel applies this regulatory theory to 3D manufacturing, arguing that it depends on certain raw materials which may be regulated because of their harmful emergent external properties. The CRISPR-Cas9 technology raw materials might be similarly regulated.

B. Nanotechnology

Nanotechnology has received significant attention from policymakers, regulators, and academic scholars over the last decade. Nanotechnology (nanotech) shares a similar regulatory space with CRISPR-Cas9 as another example of an emerging and democratized technology. Every industrial country is pursuing nanotech, but none wants to impose restrictive regulations that could slow development and impede the economic benefits.[177] Thus, an international framework has been proposed as the most promising regulatory scheme.[178] Law Professors Kenneth W. Abbott, Douglas S. Sylvester, and Gary E. Marchant have developed the most robust of the proposals.[179] Rather than initially attempting to frame an internationally binding treaty, Abbot, Sylvester, and Marchant propose the implementation of short-term strategies that feed into a midterm regulatory strategy.[180]

The proposal suggests multiple regulatory methods in the short term. The first being the creation of a body of experts to evaluate the state of the technology, its development, and related issues including its risks and benefits.[181]

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174. *Id.* at 265. Jensen-Haxel argues that regulating a raw material based on its transformative property, rather than an inherent danger, potentially leads to the regulation of innovative new products or technologies. However, should a raw material be inherently limited to transformation into a dangerous object or substance, it is permissible to regulate. *Id.*

175. *Id.* at 265–66.

176. *Id.* at 267; *see, e.g.*, *Cellulose Acetate*, ENCYCLOPEDIA BRITANNICA, http://www.britannica.com/science/cellulose-acetate (last visited Aug. 28, 2016); Roger M. Rowell et al., *Production of Dimensionally Stable and Decay Resistant Wood Components Based on Acetylation* (2008), http://www.irbnet.de/daten/iconda/CIB13122.pdf.

177. Abbott et al., *supra* note 125, at 532–33.

178. *Id.*

179. *Id.*; *See generally* Kenneth W. Abbott et al., *Soft Law Oversight Mechanisms for Nanotechnology*, 52 JURIMETRICS J. 279 (2012).

180. Abbott et al., *supra* note 125, at 532–33.

181. *Id.* at 535–36. The Intergovernmental Panel on Climate Change (IPCC) is an example of a successful body of experts, having acted as an advisor to the United Nation's Framework Convention on Climate Change. *Id.*

The proposal also suggests transgovernmental arrangements.[182] While transgovernmental arrangements must overcome the challenges of each country's differing regulatory agencies and interests, there have been some successes.[183] Two other short-term suggestions are standard setting organizations[184] and private codes of conduct.[185] Standard setting organizations traditionally form to standardize nomenclature, interoperability, and measurement.[186] However, some have engaged in "quasi-regulatory" functions by "adopting standards for environmental risk management, [occupational hazards and safety], and . . . social responsibility."[187] As the name implies, private codes of conduct are voluntarily developed by nonstate actors to regulate their own behavior.[188] The Asilomar recombinant DNA research guidelines is one example of a successful private code with its provisions later incorporated into international public policy.[189]

The medium-term regulatory suggestion is a framework convention.[190] "Framework conventions are legally binding treaties that establish limited initial obligations—typically for research, information sharing, dialogue and the like—with the expectation that the parties will add more specific substantive commitments over time. . . ."[191] Framework conventions typically allow for the efficient addition of substantive provisions in the form of protocols and other instruments.[192] States are open to these agreements because they value commitments to share information that promotes progress, the ability to consider stronger regulation when risks become clear, and procedures to negotiate substantive commitments.[193] The short-term and medium-term strategies have shown success in other areas of law and technology. However, no government has pursued this internationally by calling for an international nanotech framework, treaty, or other agreement.[194]

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182. *Id.*
183. *Id.* at 535–37.
184. *Id.* at 537–38.
185. *Id.*
186. *Id.*
187. *Id.*
188. *Id.*
189. *Id.* at 538.
190. *Id.* at 539.
191. *Id.*
192. *Id.*
193. *Id.* at 539–40.
194. Robert Falkner & Nico Jaspers, *Regulating Nanotechnologies: Risk, Uncertainty and the Global Governance Gap*, 12 GLOBAL ENVTL. POL., Feb. 2012, at 30, 46. While no nations have pushed for international nanotechnology regulations, the European Union has developed nanotechnology regulations of its own for use in both cosmetics and foods. *See* Diana Bowman et al., *Defining Nanomaterials for the Purpose of Regulation Within the European Union*, 1 EUR. J. RISK REG. 115, 116 (2010); David Azoulay & Vito Buonsante, *Regulation of Nanomaterials in the EU: Proposed Measures to Fill in the Gap*, 5 EUR. J. RISK REG. 228, 230 (2014).

IV. RECOMMENDATIONS FOR A REGULATORY FRAMEWORK

A. Private Ordering

The first option is to retain the regulatory status quo.[195] In this case, the states and regulatory bodies would determine that the national and international laws sufficiently regulate the use of the CRISPR-Cas9 technology, or that no effective regulatory model exists that excludes user autonomy. While contract is the paradigmatic private legal mechanism, other mechanisms exist, including the absence of rules and self-governing rules and norms.[196]

1. *Norms*

Industry norms are one form of private ordering. Industry norms are rules understood, accepted, and followed by industry parties as obligatory, but do not have the legal force of a state or other enforcement body.[197] In the absence of law or enforcement, norms can serve as an industry's self-regulation. While industry norms are typically unwritten and not legally binding, the consequences for breaking industry norms may result in severely negative outcomes.[198]

Industry norms require an industry culture. The lack of an industry culture may be a significant barrier to effective industry norms among CRISPR-Cas9 researchers and users as developing culture across a widely diverse group of people is difficult. This is especially true of the CRISPR-Cas9 user community given that some researchers are already conducting experiments considered dangerous and unethical to other researchers.[199] However, if the community can

195. Elen Stokes & Diana M. Bowman, *Looking Back to the Future of Regulating New Technologies: The Cases of Nanotechnologies and Synthetic Biology*, 3 EUR. J. RISK REG. 235, 235 (2012) ("[O]ne might expect that new technologies warrant new regulatory responses, especially where they are associated with new commercial applications, new exposure scenarios, new types or magnitudes of risk, or new problems of uncertainty. Experience has shown, however, that the most favourable regulatory approach is often the one that is already in place.").

196. Lucas S. Osborn, *Regulating Three-Dimensional Printing: The Converging Worlds of Bits and Atoms*, 51 SAN DIEGO L. REV. 553, 594 (2014).

197. *See* Andrew A. King & Michael J. Lenox, *Industry Self-Regulation Without Sanctions: The Chemical Industry's Responsible Care Program,* 43 ACAD. MGMT. J. 698, 701 (2000).

198. Frequently, these are negative market-based outcomes including loss of customers, loss of critical business partners, and loss of public reputation and goodwill value. It is also possible for government- funded organizations to lose their funding because of the loss of public support. *See* Deirdre Walsh & Terry Frieden, *House Passes Amendment to Cut Government Funding for ACORN*, CNN.COM, http://www.cnn.com/2009/POLITICS/09/17/house.acorn (last updated Sept. 17, 2009, 4:47 PM).

199. Katrine S. Bosley et al., *CRISPR Germline Engineering—The Community Speaks*, 33 NATURE BIOTECHNOLOGY 478, 478 (2015). Harvard geneticist George Church expressed concern after biologists at UC San Diego used CRISPR-Cas9 on fruit flies, stating that the researchers had gone "a step too far." Comparing the fruit flies to his own research with woolly mammoths, Church explained his concern with research on rapidly reproducing insects saying, "I'm afraid of everything . . . . I encourage people to be as creative in thinking about the unintended consequences of their work as the intended." Maxmen, *supra* note 86, at 63.

determine one important aspect that may be used as a lever to achieve compliance, the industry may be able to develop norms. One example is access to publishing of research findings. Publishing typically requires peer review. If the community determined that certain research was too dangerous or unethical, it may be able to convince publishers not to publish the findings by refusing to peer review the work. Publishers could also self-censor, refusing to publish the research. However, self-censorship is unlikely.[200]

Norms do not necessarily have to promulgate industry-wide. If a "critical mass" of the CRISPR-Cas9 community adopted norms, it might eventually lead to enough pressure on noncompliant parties to cease their nonnormative work, or alter their work to more closely align with the norm.

While industry norms may be effective within the research and commercial user communities, these norms have a lesser impact on the tinkerer, or hobbyist. A hobbyist[201] risks neither economic nor credential loss when using the technology nonnormatively. This is of particular importance given the democratization of the CRISPR-Cas9 technology. As the community of users broadens, forming a cohesive community and enforcing norms will become more difficult.

2. *Guidelines and Industry Standards*

Governments and governmental agencies may develop guidelines. These guidelines can provide an interpretation of the application of laws and regulations. Government guidelines do not typically carry the force of law with them,[202] and are not a form of private ordering. However, private organizations may also develop guidelines.

Guidelines developed by private organizations are another form of private ordering. "Trade associations," comprised of industry representatives, typically develop industry guidelines. Trade association members generally accept the guidelines developed by the association which serve to outline best or fair practices, and can help create industry-wide norms. Guidelines may be binding on the members of the association, but they may also be nonbinding suggestions. There are numerous conferences[203] organized by trade associations and other

200. *See* Elizabeth Weise, *Paper on Altering Bird Flu to Be Published Despite Concerns*, USA TODAY (June 21, 2012, 2:00 PM), http://usatoday30.usatoday.com/news/health/story/2012-06-20/bird-flu-vaccine/55738400/1.

201. For the purposes of this comment, "hobbyist" means any user who is not an institutional user or researcher, whose use of the technology is for personal enjoyment or whose research is personally funded.

202. CHARLES H. KOCH & RICHARD MURPHY, 1 ADMINISTRATIVE LAW AND PRACTICE § 4:60 (West, Westlaw 3d ed. Feb. 2016 update); *see also* Christensen v. Harris County, 529 U.S. 576, 587 (2000) ([I]nterpretations contained in policy statements, agency manuals, and enforcement guidelines . . . lack the force of law . . . .").

203. Some conferences dedicated to genetics and genetic engineering include the Gordon Research Conference, CRISPR Precision Gene Editing Congress, and Genome Editing Congress. *See generally About*, CRISPR CONGRESS 2017, http://crispr-congress.com/about/about/ (last visited Oct. 19, 2016); GENOME EDITING CONGRESS, http://www.genomeediting-congress.com/ (last visited Aug. 22, 2016); GORDON RESEARCH CONFERENCES, https://www.grc.org/ (last visited Aug. 22, 2016).

organizations to gather the respective community to discuss, develop, and promulgate guidelines.

Industry standards are typically more quantifiable than guidelines. Similar to the development of guidelines, standards are often developed by trade associations. Industry standards provide measurable standards to follow and may provide third-party certification. Industries will often adopt standards to garner consumer trust and to avoid burdensome governmental regulation.[204] There are some questions regarding the effectiveness of industry standards depending on the certification mechanisms.[205]

Similar to norms, standards may be imposed on research and commercial users, but are more difficult to impose on hobbyists. One means of imposing standards on hobbyists is to impose standards on the manufacturers and distributors of the raw materials. For example, because a hobbyist is not likely to make all of her own biological components, they are likely the best raw materials to standardize. However, imposing material standards may not regulate CRISPR-Cas9 use if the materials remain cheap and available.

3. *License Agreements*

Owners of proprietary technology patents may prohibit or restrict uses in their license agreements. While the development of license agreements will likely include far fewer parties than either norms or guidelines, it may have the strongest impact. Assuming that users will have to license the technology from the patent holder, the patent holder will be able to fashion a license agreement approving and disapproving of any given use of its technology. While the U.S. patent is not effective worldwide, many countries have similar intellectual property protection systems that may be exploited for this purpose. If a team of researchers patents the technology in countries worldwide, it will have the ability to determine licensable uses.[206] The issue of enforcement-dependent protection remains. However, China, one of the countries of concern,[207] is improving its

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204. Toivo Niskanen, *A Finnish Study of Self□Regulation Discourses in the Chemical Industry's Responsible Care Programme*, 21 BUS. ETHICS 77, 78 (2012).

205. While the U.S. Chemical Manufacturers Association's Responsible Care Program has been widely viewed as a success, evidence suggests that the outcomes may be a function of factors outside of the program. King & Lenox, *supra* note 197, at 713. It is suggested that guidelines and standards are mostly ineffective without explicit and serious sanctions for organizations that fail to meet them. However, the International Organization for Standards' (ISO) ISO 14001 standard, which includes third-party certification, shows evidence of success. Niskanen, *supra* note 204, at 78 (citing Matthew Potoski & Aseem Prakash, *Green Clubs and Voluntary Governance: ISO 14001 and Firms' Regulatory Compliance*, 49 AM. J. POL. SCI. ASS'N. 235, 238–39 (2005)).

206. Two researchers, Kevin Esvelt and George Church published their gene-drive/CRISPR research before it was successful to file for a patent. Esvelt claims he did so "partly . . . to block companies that might not take the same precautions." Maxmen, *supra* note 86, at 56.

207. While China has been updating its patent system to more closely reflect the United States' system, concerns regarding enforcement linger. *See* David Cyranoski, *China's Patent Boom Brings Legal Wrangles*, 492 NATURE 323, 323 (2012) (discussing a Chinese patent dispute resulting in a court ordered apology without economic damages or an injunction preventing the infringing company from continuing to use the patented process); *see also* Peter K. Yu, *From Pirates to Partners*

patent system to more closely reflect that of the United States and the United Kingdom.[208]

An issue again arises when policing unlicensed use by hobbyists. Noncommercial users are less likely to follow the license agreement, and the licensor is less likely to take action against a hobbyist whose unlicensed use has little or no commercial value.[209] Thus, license agreements providing acceptable uses for CRISPR-Cas9 may be effective to police commercial and researcher use, but are unlikely to prevent unlicensed use by hobbyists.

B. Nonbinding International Harmonization

International harmonization refers to regulatory alignment across multiple countries.[210] Harmonization typically involves an organization whose members include the regulators of their respective countries.[211] Once the organization agrees on the policies to be enacted, the individual regulators promulgate them in their respective countries.[212] Thus, the regulations are not overseen or enforced by an international organization, but by each country's respective regulatory agency.

Some international harmonization regulating CRISPR-Cas9 may be possible in the short term. For instance, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[213] is a potential organization through which pharmaceutical regulations may be developed, agreed upon, and then promulgated for implementation.[214]

(Episode II): Protecting Intellectual Property in Post WTO-China, 55 AM. U. L. REV. 901, 925 (2006).

208. Louis S. Sorell, *A Comparative Analysis of Selected Aspects of Patent Law in China and the United States*, 11 PAC. RIM L. & POL'Y J. 319, 326 (2002).

209. Rebecca S. Eisenberg, *Patent Costs and Unlicensed Use of Patented Inventions*, 78 U. CHI. L. REV. 53, 64–65 (2011).

210. *See* Abbott et al., *supra* note 125, at 536–37. *See* discussion *infra* Section IV.C (explaining that international framework conventions and treaties are forms of binding international harmonization).

211. *See* Abbott et al., *supra* note 125, at 536–37; Philip Macdonald & Stephen Yarrow, *Current Harmonization Activities Related to Risk/Safety Assessment by the OECD Working Group on Harmonisation of Regulatory Oversight in Biotechnology*, 5 ENVTL. BIOSAFETY RES. 223, 223 (2006).

212. *See* Paul M. Booth, *FDA Implementation of Standards Developed by the International Conference on Harmonisation*, 52 FOOD & DRUG L.J. 203, 205 (1997).

213. Formed in 1990, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) includes the pharmaceutical regulatory agencies in Japan, Europe, and the United States—the FDA. *History*, ICH, http://www.ich.org/about/history.html (last visited Aug. 25, 2016). In the United States, the FDA has implemented regulations developed by the ICH. Booth, *supra* note 212, at 205–08. Successful implementation of international harmonization has largely been a function of pharmaceutical companies' economic interests and to accelerate the drug approval process ensuring drugs come to market in all countries at a similar time, quieting any criticism of any one drug agency's sluggishness. *Id.* at 203, 205–208.

214. *See* Booth, *supra* note 212, at 205, 208 (explaining that the FDA has been an active participant with and adopted the ICH's guidelines).

Harmonization of CRISPR-Cas9 regulation faces similar barriers to the harmonization of nanotechnology regulation. First, CRISPR-Cas9 has a wide range of uses which are difficult to regulate through any single regulatory agency or by a general regulatory instrument.[215] The ICH may be able to harmonize regulation of the pharmaceutical applications, but would not regulate the wide range of other uses. While other harmonization organizations exist[216] and more may emerge, most countries appear disinterested in slowing biotechnological innovation.[217] However, international harmonization outside of an internationally binding instrument may be more feasible considering each sovereign's self-regulatory interests. Nevertheless, the ability of these organizations to produce and harmonize international CRISPR-Cas9 regulations is probably limited.[218]

C. Binding International Harmonization: A New International Treaty/Convention

The hope of an internationally binding treaty in the near term is unrealistic. Countries continue to show a disinterest in limiting their scientific sovereignty, instead opting to maintain control of their research policy. The existing binding treaties and conventions that address biotechnology allow each country to retain policy autonomy. Even in the face of a potential national-security threat, the United States has elected to forego negotiating an inspection regime for the BWC.[219] While there appears to be a willingness to engage in some binding agreements to share information, the willingness of the Parties to allow these agreements to control their individual state policy is fairly weak. Further, even when there are already agreements in place, parties have shown little interest in

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215. CRISPR-Cas9 shares the characteristic of wide range of uses with nanotechnology, though CRISPR-Cas9 is different because it is one specific technology and not a large assortment of technologies. Graeme A. Hodge et al., *Introduction: The Regulatory Challenges for Nanotechnologies*, *in* INTERNATIONAL HANDBOOK ON REGULATING NANOTECHNOLOGIES 3, 6 (Graeme A. Hodge et al. eds., 2010) ("'Nanotechnology' is not simply one discipline, or family of techniques, but rather a vast range of disciplines including engineering, materials science, biotechnology, medicine, physics, chemistry and information technology.").

216. For example, the OECD has a Working Group on Harmonisation of Regulatory Oversight in Biotechnology that focuses on the interaction between biotechnology and the environment to provide information and standardize the data on which regulators make policy determinations. Macdonald & Yarrow, *supra* note 211, at 223 (2006).

217. *See* Abbott et al., *supra* note 125, at 525; *see also* Matishak, *supra* note 137 ("White House officials argued that [a harmonization] system would not succeed in boosting confidence in adherence to the international agreement and would prove financially burdensome to U.S. biodefense efforts and the biotechnology industry.").

218. *See, e.g.,* Georgia Miller & Gyorgy Scrinis, *The Role of NGOs in Governing Nanotechnolgies: Challenging the "Benefits Versus Risks" Framing of Nanotech Innovation*, *in* INTERNATIONAL HANDBOOK ON REGULATING NANOTECHNOLOGIES 409, 409 (Graeme A. Hodge et al. eds., 2010) (explaining that little regulation has been applied to nanotechnology because countries are disinterested in slowing the pace of innovation and its possible benefits).

219. The United States decided to forego negotiations because of, inter alia, concerns that it would unnecessarily infringe on biotech industry growth and scientific research and development that the United States considers critical. Mark Landler, *Obama Administration Takes a New Approach to Biological Weapons*, N.Y. TIMES (Dec. 8, 2009), http://www.nytimes.com/2009/12/09/world/09biowar.html.

creating enforcement mechanisms, as has been seen with the BWC and the CBD and Cartagena Protocol.

While an internationally binding agreement to regulate the use of CRISPR-Cas9 is unlikely, many regulations may be worth considering. First, developing binding standards for the benefit of all Parties involved. Some considerations include mandatory reporting, laboratory safety, and user training requirements. However, even if a binding agreement is adopted by the majority of states using CRISPR-Cas9, it appears that few will have interest in an enforcement mechanism beyond the good faith of the Parties. It may be worth considering a shift in the goal of regulation from prohibiting certain research or uses to other goals such as continuous international awareness of the conducted research. Regardless, a restrictive treaty or convention is not likely to be feasible in the near term unless the Parties devise a novel incentive.

1. *Precautionary Principle*

The precautionary principle has been invoked in a number of treaties and conventions,[220] frequently with variations in its exact formulation.[221] Generally, the precautionary principle is an approach to risk management where the burden of proving the nonexistence of a risk to the public and the environment falls on the acting party in the absence of a scientific consensus that the action or policy is harmless.[222] The precautionary principle has been applied negatively, as an exception to allow greater restriction that would otherwise be in violation of a treaty, and affirmatively to induce action.[223]

The precautionary principle has little effect when applied negatively.[224] When applied negatively, the precautionary principle suggests that the absence of scientific certainty is not a reason to abstain from protective action.[225] However, there are reasons that parties may abstain from taking protective action aside from scientific certainty. Despite the ability of parties to claim other reasons to abstain from protective action, a negatively applied precautionary principle may provide some persuasive authority for states looking to implement an affirmative policy. Thus, while there is little legitimate power in a negatively framed precautionary principle, there are still potential benefits.

The precautionary principle can have great power when it is applied as an exception to otherwise binding restrictions. The World Trade Organization

220. The U.N. Framework Convention on Climate Change, World Trade Organization's Agreement on Sanitary and Phytosanitary Measures, Convention on the International Trade on Endangered Species, The Cartagena Protocol, Rio Declaration on Environment and Development all invoke some form of the precautionary principle. Cass R. Sunstein, *Beyond the Precautionary Principle*, 151 U. PA. L. REV. 1003, 1006, 1012, 1013, 1048 (2003); Wilson, *supra* note 79, at 353.

221. Wilson, *supra* note 79, at 352 n.265.

222. *See* World Comm'n on the Ethics of Sci. Knowledge and Tech., *The Precautionary Principle*, THE UNITED NATIONS EDUC., SCI. AND CULTURAL ORG. 12–13 (2005), http://unesdoc.unesco.org/images/0013/001395/139578e.pdf.

223. Wilson, *supra* note 79, at 352–53.

224. *Id.* at 352.

225. *Id.*

(WTO) provides an exception to its Agreement on Sanitary and Phytosanitary Measures "when 'relevant scientific evidence is insufficient' to assess particular risks to human, animal, or plant life or health."[226] The exception allows Parties to prohibit the import of otherwise acceptable products. Thus, a patchwork of trade regulations exists because of the respective sanitary standards of the different Parties.[227] This precautionary principle application allows the circumvention of binding regulations, rendering the regulations largely ineffective.

Some conventions affirmatively apply the precautionary principle in situations of uncertainty.[228] Applied affirmatively, Parties must show the risk in acting is sufficiently insignificant to meet the standard before they can act. This is a very effective method of regulation. Given the current climate, it is unlikely that Parties would agree to such an application of the precautionary principle for any biotechnology. Biotechnology is a field for which individual countries have preferred to set their own policy without giving binding authority to a larger group. In doing so, it is recommended that countries consider the precautionary principle when developing policy regarding the regulation of CRISPR-Cas9 to induce specific goals such as laboratory safety and researcher training.

2. *Composition and Function of a Body of Experts*

One possible approach is for a body of experts to have regulatory authority over the use of CRISPR-Cas9 in all countries that are Parties to the treaty/convention (Convention). The Environmental Protection Agency serves as a possible model for such a body, where the body of experts promulgates and enforces regulations according to the terms of the Convention.[229] The body of experts could apply the precautionary principle and regulate the use of CRISPR-Cas9 as necessary. Depending on the requirements of the Convention, this body of experts could emplace technical restrictions on products, require permits for certain research, prohibit certain research, institute reporting requirements and laboratory safety regulations, and impose punishment on violators regardless of whether their research causes any actual harm.

The composition of the body of experts should include CRISPR-Cas9 researchers, lawyers, government authorities, and nongovernmental organizations (NGOs).[230] Civilian representatives may be helpful in determining social norms, but it is also possible that these representatives will be alarmist and unhelpful.[231]

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226. *Id.* at 353 (citing Agreement on the Application of Sanitary and Phytosanitary Measures, art. 5.7, Marrakesh Agreement Establishing the World Trade Organization, Annex 1A, THE LEGAL TEXTS: THE RESULTS OF THE URUGUAY ROUND OF MULTILATERAL TRADE NEGOTIATIONS (1999), 1867 U.N.T.S. 493).

227. *Id.*

228. *Id.*

229. *Id.* at 355–56.

230. Gary E. Marchant & Wendell Wallach, *Coordinating Technology Governance*, 31 ISSUES SCI. & TECH., Summer 2015, at 43, 47–48. It is worth noting that in the nanotech regulatory debate NGOs have had limited success. Miller & Scrinis, *supra* note 218, at 409.

231. Two examples of popular alarmist claims do not currently comport with scientific evidence and the prevailing opinion of the scientific community include those who believe genetically modified crops are a health risk and those who believe vaccines cause autism. *See* Clyde Haberman,

Civilian inclusion through the various NGOs may be an efficient means to filter out alarmism, while ensuring the public has a voice.[232] The body of experts should also include other genetic modification and catastrophe experts.[233] Other than the civilian representatives, those considered should be best equipped to understand the complexity of the CRISPR-Cas9 technology. It is preferable to have lawyers and government representatives whose career focus includes biotechnology.

While the Convention should give the body of experts significant authority to manage CRISPR-Cas9, Parties should retain decision-making powers for any modification to the Convention. Parties should also have the power to overrule the body of experts. If the body of experts desire a Convention alteration, the alteration could become binding if agreed to by a two-thirds majority Party vote. Furthermore, if a Party wishes to override a decision made by the body of experts, the Convention should require either a majority or a two-thirds majority Party vote.

3. *Review and Enforcement Mechanism*

An effective mechanism for review and enforcement is complex and unlikely. The Parties to previous conventions and treaties have shown a disinterest in any enforcement that limits their ability to assess and determine their own policy for such technologies.[234] If the Convention were to incorporate a review and enforcement mechanism, it would require an independent body to review research requests and to determine their acceptability under the terms of the Convention. This body would also be responsible for independent laboratory reviews to assess compliance. The Convention could presume that any conducted research or use that fits under its general terms is considered acceptable unless it is determined to be unacceptable upon review. Research that falls outside of the Convention's terms may be appealed by arguing the necessity of the research and showing that the appropriate safety mechanisms are in place.

A Discredited Vaccine Study's Continuing Impact on Public Health, N.Y. TIMES (Feb. 1, 2015), http://www.nytimes.com/2015/02/02/us/a-discredited-vaccine-studys-continuing-impact-on-public-health.html (explaining that a discredited as fraudulent and withdrawn scientific study is largely responsible for the anti-vaccination movement); Emily Willingham, *The Very Real Paranoia Over Genetically Modified Foods*, SLATE (Jan. 17, 2012, 1:23 PM), http://www.slate.com/articles/health_and_science/medical_examiner/2012/01/genetically_modified_foods_ari_laux_s_alarmism_in_the_atlantic.html.

232. Miller & Scrinis, *supra* note 218, at 416–17.

233. Personally, I favor the inclusion of Dr. Ian Malcolm in all such bodies of experts. *See generally*, MICHAEL CRICHTON, JURASSIC PARK (1990) (including the character, Dr. Ian Malcom, a mathematician specializing in chaos theory, who wisely comments on the failure of man's ability to control nature).

234. Landler, *supra* note 219.

4. *Public Participation and Access to Information*

The public should have the ability to raise objections to conducted research with the reviewing body. The reviewing body may compare the submitted concerns with the scientific evidence to determine the legitimacy and possible action. A continuously refined categorization system should be developed to keep these submissions from becoming overwhelming. This system could group similar concerns together while capturing outliers that may not have popular support but are legitimate concerns, nonetheless.[235] The NGO convention advisors could be responsible for the development and management of the public input system, as they may be best suited to this responsibility.

The public should have broad access to information about the research conducted under the Convention.[236] Such information may include annual reports on safety issues related to the research, information regarding cases decided by the judicial body, and regulations imposed by the body of experts—assuming one exists. To gather sufficient and accurate information, the Convention should mandate certain reporting requirements for both the Parties and researchers. The Parties should consider creating a communications board responsible for disseminating the gathered information to societies, worldwide. Each Party should also be required to actively distribute information by the most effective means in its particular society.

5. *Regulating Scientists*

The potential benefits of CRISPR-Cas9 are great, so too are the potential risks. However, the probable occurrence of any of the risks is so insignificant that widespread use and research are greatly favored. Furthermore, users have good reason to use caution, as they will almost certainly be the first affected by any risk created. Metaphorically speaking, if the fox is watching the henhouse, it behooves the fox to ensure the hens do not lay eggs that hatch into ultraviolent, razor-sharp-clawed, laser-shooting-eyed Kodiak bears, unless those Kodiak bears are safely kept to prevent them escaping the henhouse to almost certainly cause the fox's demise. Thus, regulators should emplace limited restrictions and instead emphasize safety.

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235. Whitehouse.gov has a system that requires 150 signatures within thirty days to be searchable on whitehouse.gov, and 100,000 signatures to receive an official response. *Terms of Participation, We the People: Your Voice in Our Government*, WHITEHOUSE.GOV (Updated Oct. 22, 2014), https://petitions.whitehouse.gov/how-why/terms-participation. When a user submits a petition the system shows other petitions that may be similar so the submitter may choose to support an existing petition rather than creating a new one. *Step By Step Guide, We the People: Your Voice in Our Government*, WHITEHOUSE.GOV, https://petitions.whitehouse.gov/how-why/step-step-guide (last visited Feb. 20, 2016).

236. This recommendation stems from the concern regarding public alarmism often caused by false or misleading news reporting leading to the misinformed public possibly hijacking the process. *See* Willingham, *supra* note 231; Haberman, *supra* note 231.

6. *Summary*

There is no interest in an internationally binding treaty or convention among all of the necessary Parties. Parties have shown little willingness to engage in nonstate regulation of biotechnology. The existing treaties and conventions have no effective enforcement or means of recourse, with no indication that the Parties will agree to such a development. While it may be worth considering the content and provisions of an internationally binding treaty or convention, without a change in the current atmosphere there is little likelihood of success.

We have little choice but to trust CRISPR-Cas9 users and to know that the catastrophic, doomsday scenarios that occur in the imaginations of science fiction authors are so unlikely that they are nearly impossible. Because this technology will be used in government and nongovernment labs, as well as makeshift, unregistered labs, an international system of regulation would be largely ineffective and unfeasible. However, the users should be trusted to understand the limits needed to protect against the dangers of the technology. The concern of superbugs and posthumans should not lead governments to try to limit the distribution and use of CRISPR-Cas9 technology. Such restrictions would reduce the ability to respond to potential issues created by the use of the technology by eliminating access to one of the strongest defenses, the CRISPR-Cas9 technology itself. CRISPR-Cas9 largely serves as the solution to its own issues. A wide distribution and understanding of the technology is a valuable asset in the event of a genetically engineered or naturally arising life-based catastrophe. Sometimes the best offense is a good defense.