THE PATENTABILITY OF GENE EDITING TECHNOLOGIES SUCH AS CRISPR & THE HARMONIZATION OF LAWS RELATING TO GERMLINE EDITING

Jessica Wachowicz*

ABSTRACT

The following paper will discuss CRISPR, a process that allows for efficient gene editing, and how it may be treated by various countries in light of the Trade Related Aspects of Intellectual Property (TRIPS) Agreement and the Ordre Public doctrine. This paper will focus specifically on how lawmakers and patent offices around the world may address issues concerning the use of CRISPR for germline editing and how countries can promote uniformity while maintaining their interest in protecting the welfare of their citizens.

* Jessica Wachowicz (wachoj@uw.edu) is a third-year student at the University of Washington School of Law whose primary area of study is emerging technologies and the legal issues associated therewith.
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INTRODUCTION

Clustered Regularly Interspaced Short Palindromic Repeats (“CRISPR”) allows for the manipulation of human, plant, and animal DNA and has been praised for its potential to treat cancer, remove inheritable diseases, and improve agricultural production. CRISPR has also been criticized, as it can be applied in the germline editing process, which may lead to “designer babies” – or parents hand-selecting their child’s physical or intellectual traits. Countries will have to delineate between permissible uses of CRISPR and uses that are considered immoral in their communities. Although The Agreement on Trade-Related Aspects of Intellectual Property Rights (“TRIPS Agreement”) sets minimum standards that promote uniformity among international patent systems, an exception exists in which a country may refuse to grant a patent for an invention that is immoral or violates public order. This exception is known as the Ordre Public doctrine or the Public Order doctrine, and whether a particular invention falls within this exception will vary from one country to the next. Sections I and II of this paper will provide an introduction to patent law, the TRIPS Agreement, and the Paris Convention for the Protection of Industrial Property (“Paris Convention”). Sections III and IV will describe the CRISPR process and how it may be used in coming years. Section V will discuss the public order doctrine in greater detail and identify the ways in which TRIPS member nations have used it in the past, and Section VI will analyze the future of CRISPR in the international patent system and a potential solution for harmonizing laws pertaining to germline editing with CRISPR.

I. THE EMERGENCE OF THE PATENT SYSTEM

Patent law is a bargained exchange in which an inventor discloses to the public how an invention can be created in exchange for monopoly power over the product or invention for a specified period of time. Although allowing individuals or entities to obtain monopoly power is generally discouraged, an exception is made in the patent law system for new inventions. The policy justification behind such a system is that it encourages individuals and entities to invest in the creation of new products, which often requires significant research and development costs, time, and resources. This patent grant allows inventors to price the product in a way that will allow them to recover such costs. When the term of the patent expires, others in the community are free to produce the same product and sell it at a lower price point.

Patent law’s roots can be traced back to 500 BCE, where chefs in an ancient Greek city were able to obtain a one-year monopoly on culinary dishes they created.¹ Beginning in the 1400s, patents began to be granted for technological

¹ University of Southern California School of Law, History of Patent Law, USC GOULD ONLINE BLOG, https://onlinellm.usc.edu/resources/infographics/history-of-patent-law/.
inventions, architecture, stained glass, and more. The patent system as it exists today is heavily influenced by the Statute of Monopolies passed in 1623 by the English Parliament. The founders of the United States believed the Statute of Monopolies to be successful in promoting innovation, and thus the United States Constitution granted Congress the authority to protect rights of inventors. Only a handful of countries are without a patent system today, including South Sudan, Somalia, Afghanistan, and Myanmar.

II. TREATIES GOVERNING PATENTS

The TRIPS Agreement, administered by the World Trade Organization, is one of the most impactful treaties governing intellectual property and has been signed by 164 countries. The purpose of this agreement was to promote uniformity by creating minimum standards for the protection and enforcement of intellectual property rights, including patent rights. As innovation began to spur during the Industrial Revolution and as goods began to cross borders with greater ease, inventors sought to have their creations protected in multiple countries. Thus, a convention was held to create international standards for patents. The first international agreement established relating to intellectual property was the Paris Convention, which was signed in 1883 and still has great force in the intellectual property world today. Article 2 of TRIPS states that members shall comply with numerous provisions set forth in the Paris Convention.

The Paris Convention set forth numerous minimum standards, but it did not impose standards relating to the subject matter of patents. This was troublesome, as many countries disagreed as to what constituted patentable subject matter. For example, biotechnology and pharmaceuticals were not considered patentable by many countries, particularly developing countries, because they did not support the notion of increasing the cost of medicine or healthcare. Inconsistencies among countries lead to the Uruguay Round, negotiations to amend the Paris

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2 Id.
3 Id.
4 Id.
8 See Chow & Lee, supra note 6, at 293.
9 Id.
10 See id.
11 Id. (citing TRIPS Article 2).
13 Id.
14 Id.
Convention. These negotiations resulted in minimum standards set forth in the TRIPS Agreement that prohibited countries from denying patent protection based on the field of technology. Thus, countries could no longer deny the patentability of pharmaceuticals or biotechnologies. Although, there are some permissible exceptions in which a patent may be denied based on its subject matter. Patents can be denied for certain methods relating to medical treatment, plants and animals (other than microorganisms), and inventions that are considered “immoral” or violate “ordre public.”

III. Clustered Regularly-Interspaced Short Palindromic Repeats (CRISPR)

CRISPR, or clustered regularly-interspaced short palindromic repeats, allows for the editing of DNA. The technology has been likened to the “Find and Replace” function of a word processor, as CRISPR technology can identify problematic or disease-causing portions of an individual’s genetic code and replace or repair them. Although gene editing is not a new concept, CRISPR provides a more efficient, accurate, and cost-effective solution. Understanding the function of DNA and RNA are essential to the understanding of CRISPR technologies. DNA, which stores genetic information, has the ability to control cells through a protein synthesis process, otherwise known as gene expression. Complementary RNA strands are created for the purpose of transferring genetic code information from the nucleus to the ribosome in order to create proteins. Thus, the DNA can transmit genetic information needed for protein creation while remaining safely in the nucleus. CRISPR “was adapted from a naturally occurring genome editing system in the bacteria . . . [and in nature, such] bacteria capture[s] snippets of DNA from invading viruses and use[s] them to create DNA segments known as CRISPR arrays.” The bacteria can remember certain viruses, and, if identified in the future, can target the virus’ DNA by producing RNA from the CRISPR arrays. The bacteria uses an enzyme to cut the virus’ DNA. Researchers were able to modify RNA to include a guide sequence that targets

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15 Id. at 295.
16 Id.
18 Id. at 394.
19 Id.
21 Id.
22 Id.
24 Id.
25 Id.
specific DNA sequences.\textsuperscript{26} The modified RNA attaches to the enzyme and can locate and cut the DNA in the same manner as it occurs in nature.\textsuperscript{27} Researchers then "use the cell’s own DNA repair machinery to add or delete pieces of genetic material, or to make changes to the DNA by replacing an existing segment with a customized DNA sequence."\textsuperscript{28}

\section*{IV. Potential CRISPR Applications}

\subsection*{A. Curing Disease}

As stated previously, CRISPR technology has the ability to edit plant, animal, and human genes.\textsuperscript{29} The most promising CRISPR application in humans is the editing of genes in a way that fights disease.\textsuperscript{30} Researchers have conducted studies on mice and have corrected mutations that "cause sickle-cell anemia, muscular dystrophy, and cystic fibrosis."\textsuperscript{31} Clinical trials will soon be conducted for a technique that uses CRISPR technology to cure a rare form of blindness.\textsuperscript{32} Further, CRISPR presents possibilities to edit away inheritable diseases and congenital conditions.

\subsection*{B. Plant Life}

CRISPR can also be applied to plants to accomplish industrial tasks.\textsuperscript{33} For example, Chinese scientists are using the technology to delete genes in wheat strains in order to make the strains more resistant to certain pests.\textsuperscript{34} In 2017, Japanese researchers used CRISPR to change the color of a flower from violet to white by editing a single gene.\textsuperscript{35}

\subsection*{C. Drug Development}

Drug developers are also excited about the possibilities presented by CRISPR technology. Because CRISPR can modify hundreds of thousands of genes at one

\textsuperscript{26} Id.
\textsuperscript{27} Id.
\textsuperscript{29} Feldman, \textit{supra} note 17, at 394.
\textsuperscript{30} Id.
\textsuperscript{31} Id. at 399.
\textsuperscript{32} Id.
\textsuperscript{33} Id. at 394.
time, researchers can test for possible causes of illness with greater ease. For example, “[c]ancer cells often need to be targeted by multiple drugs, and their susceptibility may vary from patient to patient. CRISPR will permit more rapid, systematic testing and modeling of how cancers develop and how they can be defeated.”

D. Transplantation

CRISPR technology may also be used to improve the organ transplantation process. The transplantation of organs from pigs to humans has long been a concept in the medical community, but problems often arise due to certain types of bacteria found in pig DNA. CRISPR technology can potentially be used to edit the harmful bacteria out of the pig DNA so as to increase the likelihood of success in the transplantation process.

E. Germline Cell Editing

Although the discourse regarding CRISPR has been largely positive due to the potential problems it may solve, there are many who are concerned about its potential uses. Thus far, CRISPR editing techniques are “limited to somatic cells, which are cells other than egg and sperm cells. These changes affect only certain tissues and are not passed on from one generation to the next.” Altering egg cells, sperm cells, or genes in an embryo can result in such changes being passed down through generations and is known as germline editing or genome editing. Germline and genome editing have been controversial for many years, as concerns have been expressed over “eugenics and ‘designer babies’ created to maximize intelligence and attractiveness.” Although germline and genome cell editing techniques are illegal in many countries, China has evidenced a willingness to experiment in this area. In 2015, Chinese scientists attempted to use CRISPR technology to repair a gene for a blood disorder in non-viable embryos. This year, a Chinese scientist announced that he used CRISPR to alter genes in embryos that would make the babies resistant to H.I.V. The embryos were later

36 Feldman, supra note 17, at 399.
37 Id.
38 Id.
39 Id.
40 Id.
42 Id.
43 Feldman, supra note 17, at 400.
44 Id.
implanted in the mother’s womb and resulted in the birth of two twin girls.\(^{46}\) Although, this scientist, who operated in secret and published his findings via social media, received significant backlash from the scientific communities in China and around the world.\(^{47}\) The United States currently has a ban on germline editing and has stated that there should be a “broad societal consensus” on clinical uses of germline editing before the ban is lifted.\(^{48}\)

V. ORDRE PUBLIC DOCTRINE

The concept of moral utility emerged in England, as the Statute of Monopolies banned patents on inventions that were contrary to public policy.\(^{49}\) In 1883, some participants of the Paris Convention believed that patents should not “mislead the public,” and thus a compromise was made and the “ordre public” exception was incorporated.\(^{50}\) The ordre public exception was later incorporated into the TRIPS agreement in 1994 and was signed by the 182 countries that comprised the World Trade Organization.\(^{51}\)

Article 27.2 of the TRIPS Agreement states that “[m]embers may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect ordre public or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law.” No guidance is included in TRIPS as to what constitutes immorality, thus public order exclusions vary among countries.\(^{52}\) One interpretation states that an invention that falls within the ordre public exception “expresses concerns about matters threatening the social structures which tie a society together i.e. matters that threaten the structure of civil society as such.”\(^{53}\) Morality has been interpreted as the “degree of conformity of an idea to moral principles.”\(^{54}\) It is clear, based on differing cultures and societal norms, that each country will have a separate concepts of what constitutes an immoral invention.\(^{55}\) The following sections will discuss how the ordre public exception or

\(^{46}\) Id.
\(^{48}\) Id.
\(^{50}\) Id.
\(^{51}\) Id. at 747.
\(^{53}\) Id.
\(^{54}\) Id.
\(^{55}\) Id.
principles of morality have played a role in different countries’ patent systems and how, if at all, this doctrine has affected the use of CRISPR in germline editing.

A. United States

The Patent Act states that an invention must be “useful” in order to be eligible for patentability. Justice Story, a leader in developing patent law in the United States, stated in *Lowell v. Lewis* that inventions must meet a certain threshold of moral utility. Among the list of examples Justice Story gave, inventions that would “promote debauchery” or were deceptive in nature did not pass muster under the moral utility doctrine. Courts barred the patentability of a number of inventions, such as gambling machines, over the following years pursuant to Justice Story’s holding. The Supreme Court later determined that limiting the scope of patentability should be left to Congress. The Court stated that “‘inventions directed to human/non-human chimera could, under certain circumstances, not be patentable because, among other things, they would fail to meet the public policy and morality aspects of the utility requirement.’”

As stated previously, the United States currently bans germline editing and is waiting for a global consensus on the issue before deciding whether to lift the ban. The ban only applies where the edited embryo will be transplanted into a womb to be birthed. Recently, researchers were able to conduct a CRISPR study on embryos that were developed for only a few days with no intention of transplantation into a womb. This study was met with criticism, with the U.S. intelligence community deeming CRISPR a potential weapon of mass destruction.

B. Europe

The European Patent Convention and the Biotech Directive bars the patentability of many potential uses of CRISPR. Article 53(a) of the European Patent Convention states that no patent shall be granted if it is against public order or morality, including “processes for modifying the germ line genetic identity of human beings [and] uses of human embryos for industrial or commercial purposes.” Thus, under Article 53(a), the use of CRISPR on genomes would be barred. The term “use” has been debated, as some have argued that the embryos

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57 Id.
58 See id. at 748.
59 Id.
61 Id.
63 Id.
64 Id.
must be used in the inventive process to be barred, while others have argued that any process that involves or destroys an embryo is banned.66 The EU Court of Justice later clarified the clause, stating that so long as the use of the embryo is for “therapeutic and diagnostic purposes” and the invention is useful to the embryo, the invention may be patentable.67 The term “useful” was not defined.68

“The European Court of Justice recently ruled that the use of CRISPR on crops or in the drug development process need not be regulated as strictly as genetically modified organisms (GMOs)”, but the use of CRISPR on embryos has not been discussed by the Court.69

C. China

Under Article 5.1 of the CPL, it states that the patent office may not grant a patent for an invention that is against “the laws or social morality or . . . is detrimental to public interest.”70 There are no laws that prohibit CRISPR technology, thus it must be determined whether the technology is detrimental to public interest.71 A guideline used by the Chinese patent office in determining the bounds of the morality considers “social morality to be ethical or moral norms and rules generally recognized as justifiable and acceptable by the Chinese public.”72 The guidelines give examples of certain biotechnologies that would be barred from patentability, such as editing the genes of animals in a way that causes suffering without medical benefit to humans or animals, cloning humans, or using human embryos for industrial or commercial purposes.73 The guidelines state that any process that modifies a human’s genetic identity is barred from patentability, but no law exists in china governing the use of CRISPR.74 Chinese law technically bans gene editing on human embryos, but most researchers have been able to conduct experiments with CRISPR by using non-viable embryos or cloned embryos.75

Many patent applications regarding the use of CRISPR have been submitted to the Chinese State Intellectual Property Office thus far.76 As stated previously,

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66 Id. at 7–8.
67 Id. at 8.
68 Id.
71 Id.
72 Id.
73 Id.
74 Id.
75 See Skye Gould & Kevin Loria, This map shows were researchers might design the first genetically engineered baby, BUSINESS INSIDER (Oct. 20, 2015), www.businessinsider.com/what-countries-allow-researchers-to-edit-human-embryos-2015-10.
76 See Peng, supra note 67.
China has been testing the use of CRISPR on non-viable embryos.\textsuperscript{77} Recently, a group of researchers cloned embryos that contained a blood disorder.\textsuperscript{78} Using CRISPR, the researchers were able to cut the problematic genes and replace them with other genetic material.\textsuperscript{79} Chinese researchers are continuing to conduct these studies, despite concerns over whether the technology will be patentable.\textsuperscript{80}

VI. Harmonizing the Treatment of Gene Editing Technologies

At present, countries take different approaches in applying the ordre public doctrine to cases involving germline editing. In Japan, the patent office examines scientific guidelines pertaining to stem cell research in rendering its decisions.\textsuperscript{81} Others simply look to the values held by that particular country in determining whether the invention would benefit society.\textsuperscript{82}

Looking at the values held by a particular community will lead to varying results. Some countries may value the welfare of individuals over the progression of science.\textsuperscript{83} Others argue that because these inventions can dramatically improve healthcare, and because healthcare is a human right, this public interest should override any bans on germline editing.\textsuperscript{84}

A similar dispute arose under TRIPS with respect to pharmaceuticals. As stated previously, some countries, India in particular, argued that patenting pharmaceuticals was immoral because it raised the cost of healthcare.\textsuperscript{85} In 2016, the World Health Organization published the “Guidelines for the examination of patent applications relating to pharmaceuticals.”\textsuperscript{86} The purpose of this guideline was to assist legislators in crafting laws that would allow for the patentability of pharmaceuticals generally, while imposing limitations that would prevent healthcare from becoming unaffordable.

One plausible solution is for the World Health Organization to create a set of guidelines for determining the patentability of technologies such as CRISPR. The guideline can look to other international treaties that focus on the preservation of human rights and the improvement of healthcare.\textsuperscript{87} By encouraging countries to take these agreed upon policy objectives into consideration when examining these controversial patents, results among different patent offices may be slightly less varied. A guideline from the World Health Organization (WHO) or a similar

\textsuperscript{77} Feldman, supra note 17, at 400.
\textsuperscript{79} Id.
\textsuperscript{80} Id.
\textsuperscript{81} See Prifti, supra note 57, at 13.
\textsuperscript{82} Id. at 12.
\textsuperscript{83} Id. at 14.
\textsuperscript{84} Id.
\textsuperscript{85} See Jakob Wested & Timo Minssen, TRIPS and the Life Sciences - Perspectives on Limitations to Patentability (Univ. of Copenhagen Faculty of L. Research Paper No. 2017-37, 2017)
\textsuperscript{86} Id.
\textsuperscript{87} See Prifti, supra note 57, at 12.
organization may assist countries’ legislatures in crafting laws that allow for progression in this field of science while protecting their communities from potential human rights violations, such as the destruction of viable embryos.

Attempts at harmonization have been made in the past. There are currently numerous international instruments that prohibit inventions involving genomes, such as the UNESCO Universal Declaration on Bioethics and Human Rights and the Oviedo Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biotechnology and Medicine: Convention on Human Rights and Biomedicine.\(^8\) The former states that public welfare should be prioritized over the progress of science, and the latter states that genetic modification techniques should only be allowed if “serious hereditary sex-related disease[s] [are] to be avoided.”\(^9\) These agreements make clear that public welfare is of primary importance, and that germline editing techniques should only be applied where serious risks can be avoided. The Oviedo Convention limited the scope of the exception to the avoidance of sex-related diseases, but perhaps with the introduction of CRISPR, countries may need to consider the circumstances under which genome and germline editing may be permissible.

**CONCLUSION**

In summary, relying on the ordre public doctrine to determine the patentability of CRISPR technology will lead to dramatically varying results around the world. The need for a more harmonized approach is present. Despite countries’ general avoidance of genome and germline editing, technology has developed in such a way that these practices may be highly beneficial to public welfare. Countries should reconsider their stances on such practices in light of the potential benefits CRISPR technology can offer and should attempt to reach a general consensus on the proper uses of CRISPR. Given recent events, the WHO should promptly issue guidelines to assist legislatures in crafting laws that promote progress in this area while maintaining consistency with concepts of morality.

\(^8\) Id. at 13.

\(^9\) Id.