TALLINN UNIVERSITY OF TECHNOLOGY
School of Business and Governance
Department of Law

Patrik Julius Mikkola

Comparative analysis of EU and US patent regulations on Human Embryonic Stem Cells

Master's thesis

Programme: Law, specialisation: Law and Technology

Supervisor: Pawan Kumar Dutt

Tallinn 2022

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Patrik Julius Mikkola .....
(signature, date)
Student code: 214727HAJM
Student e-mail address: patrikmikkola@gmail.com

Supervisor: Pawan Kumar Dutt
The paper conforms to the requirements in force

……
(signature, date)

Chairman of the Defence Committee:
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……
(name, signature, date)

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ABSTRACT

Within the last few decades new emerging technologies have brought a rapid increase to the development in the medical industry. As a result of these new technological advancements, stem cell research has arisen as one of the leading fields. Human embryonic stem cells, a form of stem cell, have the ability to multiply stem cells or differentiate into other types of cells, which has already resulted in major medical advancements with the potential to further improve current treatments.

Due to the costs associated with researching and developing human embryonic stem cell inventions, pharmaceutical companies are attempting to fully protect their inventions through patents. In order to protect their inventions, intellectual property and stakeholders' interests, pharmaceutical companies are seeking the maximum protection obtainable in different jurisdictions. Therefore, this study will focus on how human embryonic stem cell inventions and processes are patentable in the European Union and the United States of America.

The study will compare the two patent frameworks through their legislation, case law and relevant academic articles. SARS-CoV-2 vaccines will be used as an example throughout in order to demonstrate the similarities and differences between the two jurisdictions. The study found that human embryonic stem cell inventions are patent ineligible in the European Union whilst being patent eligible in the United States. However, ambiguity remains as to the extent of the patent eligibility in the United States. Through these findings, improvements and amendments to the patent frameworks are needed in order to provide clarity on their patentability.

Keywords: Human Embryonic Stem Cells, Biotechnology Patentability, SARS-CoV-2 Patents

ABBREVIATIONS

CJEU - Court of Justice of the European Union

ECJ - European Court of Justice

EC - European Commission

hESC - Human Embryonic Stem Cells

EPO - European Patent Office

TRIPS - Trade Related Aspects of Intellectual Property Rights

USPTO - United States Patent and Trademark Office

WTO - World Trade Organization

INTRODUCTION

The medical industry has been advancing technologically at a pace that is often difficult to keep up with from a legislative perspective. This is especially the case within the last few decades with new methods of research emerging which are changing our views on the possibilities of medical therapeutics. A major example of this has arisen with stem cells, as the potential benefits of utilising them seem to be almost endless. Stem cells have two basic properties, self-renewal and the ability to differentiate into different cells[1]. Therefore, the use of stem cells can be seen as the leading tool for regenerative medicines. However, with these benefits come equal complications as the main method of obtaining stem cells is through the destruction of embryos.

Human embryonic stem cells present the leading potential for the stem cell field, thus the research questions are: *to what extent human embryonic stem cell inventions and processes are patentable in the European Union and the United States of America? Furthermore, how has this affected the patentability of SARS-CoV-2 vaccinations which utilise human embryonic stem cell technologies?*

In order to answer this, first the study will give a general contextual explanation of what human embryonic stem cells are and how they are currently being used. As the topic of human embryonic stem cells (herein referred to as "hESC") is part of a complicated scientific field of research, this chapter will give a general understanding without attempting to explain the specific details as they fall outside of the scope of this study. However, the section will provide a general understanding of hESC in order to fully discuss the patentability of hESC related inventions in further chapters.

Following a general study of the human embryonic stem cell, the study shall proceed to compare the patent frameworks of the European Union and United States of America in relation to hESC

[1] Fico, A., Fiorenzano, A., Pascale, E., Patriarca, E.J. and Minchiotti, G., 2019. Long non-coding RNA in stem cell pluripotency and lineage commitment: functions and evolutionary conservation. Cellular and molecular life sciences, 76(8), pp.1459-1471. New York: Springer.

inventions. To do this, the chapter shall focus on the legal framework of the European Union, and subsequently separately, the legal framework of the United States of America. To determine the patent eligibility of hESC related inventions, this chapter shall explore directives, regulations, scientific articles and case law to show how hESC related inventions are currently handled within these legal frameworks.

After the legal framework has been analysed, the example of Covid-19 vaccines shall be used to compare the two legal frameworks further. This example has been chosen due to its current relevance, as well as due to the controversy that has surrounded the vaccines' use of human embryonic stem cells. Although the study will not focus on the ethics and moral viewpoint of developing and producing the vaccine or hESC research, this section will provide a general understanding of what hESC cell lines are being used in the three chosen vaccines. These are the BioNtech and Pfizer vaccine, Moderna vaccine and Janssen Pharmeceutica vaccine. The choice was made based on their general widespread utilisation and availability in the two jurisdictions that are being compared. The section will also detail how the hESC cell lines are being used in each vaccine as well as which patents the vaccine producers have currently managed to secure. Importantly this section aims to answer the question, how do Covid-19 vaccines achieve protection of Intellectual Property despite the use of human embryonic cells? Furthermore, the section will analyse the effect that the differences in patent frameworks has on the intellectual property rights of the vaccine producers, both in the jurisdictions chosen and on an international level.

Following this, the study shall also focus on the patent waivers that have recently been widely discussed with regard to the Covid-19 vaccines. The purpose of such a waiver would be to grant the general public easier access to the vaccines as a result of numerous additional manufacturers being able to start production as a result of the patent waivers. However, this study will also discuss how these patent waivers affect the rights of the Covid-19 vaccine producers. As the aim of the patent waiver is to temporarily remove the intellectual property rights of the vaccines, this section will analyse in which manner this could be done as well as the effect this will have on the vaccine manufacturers due to their patent eligibility differences. This section will also discuss further methods, which have not been considered by the World Trade Organisation or in the

patent waiver itself, which have been considered in different academic discussions attempting to suggest methods to determine a manner of balancing the rights of all parties.

Finally, the study, based on the information in the sections previously mentioned, will provide a comparative analysis on the two legal frameworks in the European Union and the United States of America. This will compare all the previous findings to determine how the patent eligibility of hESC related research differs in the two legislations, as well as provide case law and examples to further exemplify this difference. The aim will be to determine the main similarities and differences to the approach of protecting intellectual property by patenting hESC inventions in order to provide suggestions for future improvements to the patent frameworks. This will be done through analysing the comparison and providing suggestions based on the missing elements of each patent framework.

Future technologies in human embryonic stem cell research will also be considered, as current technologies may only be able to utilise hESC to a certain degree due to the limitations of patentability worldwide. As the medical research field advances in the capabilities of using human embryonic stem cells, the degree to which they are used in biotechnological inventions is highly likely to increase. It is therefore timely to consider future improvements to both patent frameworks, which may assist in the preparation for these advancements.

As the field of human embryonic stem cell research is a complicated biotechnological field of research, the details and depth of the technical aspects this study is able to assess is limited. Instead, the study shall focus on the legal aspects in relation to the patentability of human embryonic stem cells. However, a certain level of biotechnological specific research and technical explanation is presented in order to give a general understanding of the topic in order that the discussions regarding the legal aspects will be full and coherent. As the human embryonic stem cell field of research is constantly developing and biotechnology researchers themselves do not have a full understanding of the limits to the applicability of the cells, the research conducted in this study is limited to a certain degree due to the complexity of the topic as well. In order to address this research limitation, a varying and greater quantity of leading academic sources will be used to show the current understanding of hESC cell research.

1. Chapter 1: Human Embryonic Stem Cells

The use of Human Embryonic Stem Cells has shown a significant amount of promise for various diseases, as discussed in the article *The Tumorigenicity of human embryonic stem cells*[2]. The authors bring attention to the potential effectiveness of the cells. Human Embryonic Stem Cells are pluripotent stem cells extracted from the inner cell mass of a blastocyst. As this definition is provided through the use of many medical terms it is important to clearly define each section. Firstly, pluripotent stem cells are cells that are able to develop into a variety of different cells. As the focus is on *Human* embryonic stem cells, pluripotent stem cells mean cells that can develop into, for example neural, cardiac, blood and most other cells in the body. The blastocyst is the fertilised egg on roughly the fourth to sixth day, where the blastocyst has an inner and outer cell mass. The outer cell mass protects the inner cell mass which contains a group of cells that will become the embryo.

There are other methods of obtaining stem cells that do not involve destroying the blastocyst. Stem cells can be obtained through both Adult Stem Cells and Perinatal Stem Cells as well. Adult Stem Cells can be found in skin tissue, bone marrow and adipocyte[3] cells from adult humans. Perinatal Stem Cells are found in perinatal tissue, for example the umbilical cord. The main issue with embryonic stem cells, from a moral point of view, is that the embryo must be destroyed in order to extract the stem cells. Therefore, the question arises as to why researchers use embryonic stem cells over adult and perinatal stem cells.

First, perinatal stem cells are limited in supply, making them unavailable for large scale research purposes[4]. There are a few reasons embryonic stem cells are so valuable for research purposes in comparison to adult stem cells. Adult stem cells are found to be less versatile and durable in

[2] Blum, B. and Benvenisty, N., 2008. The tumorigenicity of human embryonic stem cells. *Advances in cancer research*, *100*, pp.133-158. Amsterdam: Elsevier.
[3] Ilic, D., Devito, L., Miere, C. and Codognotto, S., 2015. Human embryonic and induced pluripotent stem cells in clinical trials. British medical bulletin, 116(1), pp.19-27.
[4] Balbi, C. and Bollini, S., 2017. Fetal and perinatal stem cells in cardiac regeneration: Moving forward to the paracrine era. Placenta, 59, pp.96-106. Paris: Elsevier.

comparison to embryonic stem cells[5]. This is believed to be due to the fact that adult stem cells are not as pluripotent as embryonic cells, meaning they do not have the ability to become every form of cell. There is also a higher risk of abnormalities with adult stem cells, making them more complicated to utilise than embryonic stem cells. Thus researchers require embryonic stem cells for research, especially in certain fields of research in which pluripotent cells are required.

Human embryonic stem cells are one specific classification of embryonic stem cells being used for research in general. Embryonic stem cells can be obtained from the blastocysts of different animals, for example most commonly mice and monkeys. These embryonic stem cells are used for mainly the same purposes as human embryonic stem cells, however lack some of the range of applications and potential applications[6]. Therefore, this study will focus on human embryonic stem cells and their legal status without consideration for the utilisation of other types of embryonic stem cells. The main discussion topics related to hESC research and development are usually related to the ethics, morals and values that surround the sensitive topic. Although this paper will discuss this area briefly, the scope of the study shall however focus on the patentability and legal status of hESC research and development.

The use and effect of using human embryonic stem cells has shown great promise in the medical field both practically and theoretically. Even as early as 1998, Thomson wrote that during his lifetime he would witness diseases being cured by these therapies[7]. This shows the lifespan and speed of development of human embryonic stem cell research, as only just over two decades ago researchers were only at the optimistic wishful preliminary stage with hESC research. In 2016 a significant breakthrough was made using hESC, where the ability to recreate clean blood cells for the purpose of blood transfusions was made possible[8]. Due to the technical difficulty of research in this field, research and development can be very expensive[9]. For this reason many

[5] Singh, A., Yadav, C.B., Tabassum, N., Bajpeyee, A.K. and Verma, V., 2019. Stem cell niche: Dynamic neighbor of stem cells. European journal of cell biology, 98(2-4), pp.65-73. Amsterdam: Elsevier.
[6] Nakamura, T., Fujiwara, K., Saitou, M. and Tsukiyama, T., 2021. Non-human primates as a model for human development. Stem cell reports, 16(5), pp.1093-1103. Tokyo: Elsevier.
[7] Geesink, I., Prainsack, B. and Franklin, S., 2008. Stem cell stories 1998–2008. *Science as Culture*, *17*(1), pp.1-11. Oxfordshire: Taylor & Francis.
[8] Migliaccio, A.R., Whitsett, C., Papayannopoulou, T. and Sadelain, M., 2012. The potential of stem cells as an in vitro source of red blood cells for transfusion. *Cell stem cell*, *10*(2), pp.115-119. Amsterdam: Elsevier.
[9] Golchin, A., 2021. Cell-based therapy for severe COVID-19 patients: clinical trials and cost-utility. *Stem cell reviews and reports*, *17*(1), pp.56-62. Singapore: Springer.

research organisations will wish to protect their developments through intellectual property rights. This study will later focus on the intellectual property that hESC related research and developments are able to protect, as well as a comparison between the options within the European Union's and United States' frameworks.

2. Chapter 2: Patentability of Human Embryonic Stem Cells

Having established the scientific context for human embryonic stem cells, this chapter will focus on the comparison between the patentability of hESC related inventions between the European Union and the United States of America. First, a comprehensive analysis of the two legal frameworks will be conducted, with a comparison of the two frameworks presented in Section 2.3.

2.1. European Union framework

In the European Union, the limitation to patent eligibility created in the Strasbourg Convention of 1963 has remained at a key role in the patent structure of human embryonic cells since[10]. This exception was first listed in Article 2(a) of the Convention, stating that contracting states shall not be bound to provide patents for inventions of which the exploitation or publication would conflict with *ordre public* or morality. This article from the Convention is remarkably broad, leading to its possible interpretation in multiple different manners. Interestingly, this clause has been used throughout the history of the European Union with only a few minor changes despite its ambiguous and broad wording.

Following the Strasbourg Convention Article 2(a), the European Patent Convention (hereinafter "EPC") was agreed upon in 1973 The EPC had a similar section to that in the Strasbourg Convention, as Article 53 (a) EPC 1973. This stated that patents shall not be granted for "*inventions, the publication or exploitation of which would be contrary to "ordre public" or*

[10] O'Sullivan, M., 2019. Biotechnology, Patents and Morality: A Deliberative and Participatory Paradigm for Reform. Routledge: Taylor & Francis.

morality, provided that the exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States". One of the main issues that arises from this exception, is the lack of term definitions. Examples of such ambiguous terms are: "ordre public" and "morality" which have been provided with no specific definitions[11].

As a result, almost two decades later, case law began addressing the lack of clarity of the terms. The case T 356/93 *PLANT GENETIC SYSTEMS N.V. v. Greenpeace Ltd.* consisted of an anti-herbicide plant gene patent that Plant Genetic Systems owned. This would make the plant resistant to herbicides once applied by a particular method.

In making their decision, the Board of Appeals of the EPO clarified the two concepts, "ordre public" and "morality" in the context of Article 53 (a) EPC 1973. The EPO clarified that *ordre public* should be construed as "*under Article 53(a) EPC, inventions the exploitation of which is likely to breach public peace or social order (for example, through acts of terrorism) or to seriously prejudice the environment are to be excluded from patentability as being contrary to ordre public.*"

As for the concept of morality, the EPO clarified their definition in accordance with "*Article 53(a) EPC, inventions the exploitation of which is not in conformity with the conventionally-accepted standards of conduct pertaining to this culture (European society and civilisation) are to be excluded from patentability as being contrary to morality*.

These definitions provided by the EPO did not coherently define the terms to the extent that would be needed when determining the patentability of certain subject matters, especially when these were regarding new complicated processes or matters such as stem cells. Therefore, the early human embryonic stem cell inventions would have been judged for their patent eligibility based on this criteria. As a result, the Biotechnology Directive was enforced in 1998 to close the gap in uncertainty especially in the terms ordre public and morality.

[11] Cippitani, R., 2019. Ethical issues and law-making power: how European case law has rewritten Italian law on medically assisted reproduction. Monash bioethics review, 37(1), Springer, pp.46-67

2.1.1 Biotechnology Directive

The European Union Biotechnology Directive (Directive on the Legal Protection of Biotechnological Inventions 98/44)[12] was made to ensure a European Union harmonised approach to the protection of biotechnological inventions[13]. The Biotechnology Directive is the first direct action the EU has taken in relation to the patentability of human embryonic stem cells. Importantly, Article 6(1) of the Directive follows the same precedent set through the Strasbourg Convention, stating that "*Inventions shall be considered unpatentable where their commercial exploitation would be contrary to ordre public or morality (...)*". However, the difference with the Biotechnology Directive and the aforementioned Conventions is found in section 6(2) of the Biotechnology Directive. Section 6(2) provides specific examples that do not qualify for patents, importantly 6(2)(c) which states:

2. On the basis of paragraph 1, the following, in particular, shall be considered unpatentable:

c. uses of human embryos for industrial or commercial purposes;

However, the mention of human embryos causes one of the main criticisms of the EU patent structure regarding stem cells. The Biotechnology Directive does not contain a specific definition for the human embryo, therefore causing confusion as to when the ovum should be considered a human embryo. In the European Union it is common practice in the medical field of research to consider the embryo a human embryo after fourteen days from the day of fertilisation[14]. The importance of when it is considered a human embryo is crucial for the patentability of any related subject matter. If the embryo is not considered a human embryo for any period of time, it could allow for patent eligibility of at least a certain amount of hESC related inventions in accordance with the Biotechnology Directive[15].

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[12] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions

[13] Jiang, L., 2020. Biotechnology Directive: A Major Step in Biotechnology Patent Law in Europe. In Bioeconomy for Sustainable Development (pp. 143-158). Springer, Singapore.

[14] Lovell-Badge, R., Anthony, E., Barker, R.A., Bubela, T., Brivanlou, A.H., Carpenter, M., Charo, R.A., Clark, A., Clayton, E., Cong, Y. and Daley, G.Q., 2021. ISSCR guidelines for stem cell research and clinical translation: the 2021 update. Stem cell reports, 16(6), pp.1398-1408. Amsterdam: Elsevier.

[15] Directive 2001/83/EC arts 6, 10; Directive 2004/27/EC art 10(4); Julian Hitchcock and Clara Sattler de Sousa e Brito, 'Case Comment: Should Patents Determine when Life Begins?' (2014) 36(6) EIPR 390, 395.

2.1.2 Brüstle v Greenpeace

In the case C-34/10 Brüstle v Greenpeace, the German Bundesgerichtshof referred the case to the ECJ for a preliminary ruling regarding, among other aspects, the definition of the human embryo under the Biotechnology Directive. In the case, a German Professor filed a patent application for their method of converting human embryonic stem cells into neural precursor cells that could treat diseases such as Parkinson's. Greenpeace sought to annul the patent through the use of the exclusion of patentability provided in Biotechnology Directive Article 6(2) "uses of human embryos for industrial or commercial purposes"[16].

The two questions that made the discussion a landmark case were the following:

1. Does the prohibition extend to a blastocyst, which has lost its ability to become a human being?
2. Is a matter unpatentable even if the use of human embryos does not form part of the technical teaching claimed with the patent, but is a necessary precondition for the application of that teaching?

The Advocate General responded by stating that "*an invention must be excluded from patentability where the application of the technical process for which the patent is filed necessitates the prior destruction of human embryos or their use as base material, even if the description of that process does not contain any reference to the use of human embryos*".

For the definitions, Human Embryos were defined as "*any human egg cell must, as soon as fertilised, be regarded as "human embryo*", since fertilisation commences the process of development of a human being". For Industrial or commercial purposes, this should "*also cover the use of human embryos for purposes of scientific research*"[17].

[16] Mansnérus, J., 2015. Brüstle v. Greenpeace: Implications for Commercialisation of Translational Stem Cell Research. European Journal of Health Law, 22(2), pp.141-164. Leiden: Brill.
[17] Cuchiara, M.L., Lawford Davies, J. and Matthews, K.R., 2013. Defining "research" in the US and EU: contrast of Sherley v. Sebelius and Brüstle v. Greenpeace rulings. Stem Cell Reviews and Reports, 9(6), pp.743-751. New York: Springer.

This clarification by the Advocate General seems to almost completely prohibit the patenting of any hESC inventions, even if they are only hESC-based[18]. The case has become an intellectual property law landmark case for any hESC related activities, and is still being used to evaluate and interpret cases that fall under the Biotechnology Directive Articles 6(1) and 6(2)[19].

2.1.3 TRIPS

The agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) is an integral part of European Union Intellectual Property Law. Under TRIPS, patents shall be available for all inventions. This is in severe conflict with the Biotechnology Directive in the European Union. This can be found in Article 27(1):

"*Patents shall be available for any inventions, whether products or processes, in all fields of technology, provided they are new, involve an inventive step and are capable of industrial application. Patents shall be available and patent rights enjoyable without discrimination as to the place of invention or the field of technology.*"

This would appear to cause conflict, however Article 27(2) provides an exclusion to the prior Article[20]:

"*Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect ordre public or morality.*"

In the European Union, this means that Article 6(1) of the Biotechnology Directive is applicable despite TRIPS. This has also been clarified by the CJEU in C-414/11 Daiichi Sankyo v Sanofi-Aventis Deutschland, in which they stated that Article 27(2) TRIPS allows members to

[18] Giles, J., 2012. Brüstle v Greenpeace eV: (Case C-34/10): Court of Justice of the European Union (Grand Chamber): Skouris President, Tizzano, Cunha Rodrigues, Lenaerts, Bonichot, Safjan (Rapporteur) Presidents of Chambers, Prechal, Rosas, Silva de Lapuerta, Schiemann, Šváby, Berger, Jarašiūnas, JJ: 18 October 2011. *Oxford Journal of Law and Religion*, *1*(2), Oxford University Press, pp.528-529.

[19] Farrand, B., 2016. Human embryonic stem cells and patent law in the EU and China: convergence in standards through divergence in institutions. *Intellectual Property Quarterly*, *3*, Sweet & Maxwell, pp.260-277.

[20] Chuma-Okoro, H. and Oluwasemilore, I.A., 2022. Intellectual property rights, agricultural biotechnology and food sufficiency: strengthening the Nigerian intellectual property legal framework for food self-sufficiency in the aftermath of a global pandemic. International Review of Law, Computers & Technology, pp.1-20. Oxfordshire: Taylor & Francis.

exclude patentability for public interest reasons, which the EU practices through Article 6(1) of the Biotechnology Directive.

2.2 United States Framework

Certain Member States of the European Union have deep religious roots. As a result, the EU has a more conservative approach towards hESC cell research. However, the United States of America seems to have a more liberal approach in their patent framework[21], which is why a comparison should be drawn.

In the United States of America, the patentable material is mainly defined under 35 U.S.C. §101 [22]. This states that "*Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.*" The Supreme Court limited the scope of its definition of patentable material by adding three exceptions, laws of nature, physical phenomena and abstract ideas. The main issue is that no specific reference to human embryonic stem cells or embryonic stem cells was made related to the matter of patent-eligibility[23].

The key related legislation, the Leahy–Smith America Invents Act sec. 33(a), 125 Stat. 284, states that "*Notwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a human organism.*" The act leads to the discussion of whether hESC cell research should be classified under this section, as although in general hESC cell research is derived from *human organisms*, in the majority of hESC uses the cells are not extracted in the later stages. In general the hESC cells are removed or used in the testing phases, which lead to a

[21] Jaffe, A.B., 2000. The US patent system in transition: policy innovation and the innovation process. Research policy, 29(4-5), pp.531-557. New York: Elsevier.
[22] Hamidinia, S., 2019. Courts continue to clarify what is patent eligible subject matter. Journal of Generic Medicines, 15(4), pp.203-206. Washington DC, Sage.
[23] Lovell-Badge, R., Anthony, E., Barker, R.A., Bubela, T., Brivanlou, A.H., Carpenter, M., Charo, R.A., Clark, A., Clayton, E., Cong, Y. and Daley, G.Q., 2021. ISSCR guidelines for stem cell research and clinical translation: the 2021 update. Stem cell reports, 16(6), pp.1398-1408. Berkeley, Elsevier.

further clarification in the Leahy–Smith America Invents Act stating that "*The U.S. Patent Office has already issued patents on genes, stem cells, animals with human genes, and a host of non-biologic products used by humans, but it has not issued patents on claims directed to human organisms, including human embryos and fetuses. My amendment would not affect the former, but would simply affirm the latter.*"[24] Human embryos are non-patent eligible, however are required to be destroyed in order to obtain human embryonic stem cells.

In the United States of America, the egg is considered an embryo for the first fourteen days[25]. After this period, the embryo becomes defined as a human embryo. This is justified by the conclusion that the embryo should develop a certain amount before it can be considered human. This justification is based on what is often referred to as the 14-day rule. The distinction in definitions will be further outlined in section 2.3, however, first it is important to analyse the legal framework of the United States to understand this distinction in further detail.

2.2.1 Diamond v. Chakrabarty

In the United States, the turning point for biotechnological intellectual property innovation began in 1980 with the Diamond v. Chakrabarty case. This became the landmark case for U.S. patent law due to the resulting judgement ruled by the Supreme Court. Chakrabarty, while working at General Electric, invented a bacterium that was capable of digesting crude oil. GE applied for a patent for the bacterium with Chakrabarty as the inventor, however the application was declined by the patent examiner. At the time it was generally understood that living things were generally not patent applicable matters.

The Supreme Court ruled in favour of Chakrabarty as they found that the bacterium that was invented was characteristically different from any bacteria found naturally. As it was beyond any of the limitations listed previously, it was found to be patent-eligible. Thus, a general

[24] 157 Cong. Rec. E1177-04 (testimony of Representative Dave Weldon previously presented in connection with the Consolidated Appropriations Act, 2004, Pub. L. 108-199, 634, 118 Stat. 3, 101, and later resubmitted with regard to the AIA; see 149 Cong. Rec. E2417-01)

[25] Peters, T., 2021. Keep the 14-Day Rule in Stem Cell Research. *Theology and Science*, *19*(3), pp.177-183. Oxfordshire: Taylor & Francis.

consensus arose that "*anything under the sun made by man*" would be patent-eligible. Although this is a vastly over-simplified statement, the case exemplifies the views of the United States as to the broad scope of their patent-eligible matters[26].

The Diamond v. Chakrabarty case has become a heavily discussed precedent as it is already over 40 years old, however it serves as the foundation on which United States patent laws were made in regards to biotechnology intellectual property. However, a less commonly known, but equally important case regarding biotechnology patentability is the *In Re Bergy* case. Similarly to the Diamond v. Chakrabarty case, the case regarded a patent application that failed on the grounds of a product of nature. Through the appeal process, the United States Court of Customs and Patent Appeals reversed the decision made by the United States Patent and Trademark Office. This was done on the grounds that the fact that the organism was living does not affect the patentability, instead proof that the organism was not naturally occuring was required in order to satisfy the patent eligibility. A living organism is a very broad term, therefore the patentability of human embryonic stem cells or even stem cells in general is not necessarily clear or straight-forward based on these precedents alone.

2.2.2 Issued Patents

After the aforementioned landmark cases in *Chakrabarty* and *In Re Bergy*, the USPTO began issuing stem cell related patents quite freely. Since these cases, more than 1000 stem cell related patents have been issued. As shown by Sarah Fendrick and Donald Zuhn in their study on the patentability of stem cells in the United States of America, "*The first stem cell patents were directed to hematopoietic stem cells (e.g., U.S. Patent Nos. 5,436,151 and 5,670,147), (...) The first human embryonic stem cell patents were U.S. Patent Nos. 5,843,780, 6,200,806, and 7,029,913*[27]".

[26] Then, S.N., 2004. Stem cell technologies: regulation, patents and problems. *Journal of law and medicine*, *12*(2), SAGE, pp.188-204.
[27] Fendrick, S.E. and Zuhn, D.L., 2015. Patentability of Stem Cells in the United States. *Cold Spring Harbor Perspectives in Medicine*, *5*(12). New York: CSHPress.

James A. Thompson was the first to receive human embryonic stem cell patents in the United States, as previously mentioned. The earliest of these date to 1995, which shows the patent eligibility of hESC related inventions spanning only just over the last two decades. However, it is evident that hESC related patents still have their limitations due to the nature of hESC and its source.

2.2.3 Mayo Collaborative Services v. Prometheus Laboratories INC.

As human embryonic stem cell research is derived from obtaining pluripotent cells from a human blastocyst, one of the main difficulties with the patent eligibility is proving its derivation from the laws of nature[28]. In order to define the patent eligibility of hESC related inventions, the Supreme Court defined certain criteria in a couple of landmark cases.

This first came through the *Mayo Collaborative Services v. Prometheus Laboratories INC.* case in 2012. This case became a major discussionary topic amongst patent lawyers and academics of the field of research due to the controversial ruling by the Supreme Court. The case between the two parties (hereinafter "Mayo" and "Prometheus") was a dispute arising from the three patents that Prometheus owned. Prometheus was selling diagnostic kits based on their three patents to Mayo, however after a few years Mayo began selling their own diagnostic kit to its customers. Therefore Prometheus claimed that Mayo was infringing upon their patent rights. Mayo, in response, claimed that the three patents were not patent eligible according to 35 U.S.C. §101.

The dispute eventually ended up in the Supreme Court, who began interpreting the patents and their eligibility and distinction from the laws of nature. The Supreme Court stated that "*because methods for making such determinations were well known in the art, this step simply tells doctors to engage in well-understood, routine, conventional activity previously engaged in by scientists in the field. Such activity is normally not sufficient to transform an unpatentable law of nature*

[28] Martinho, A.M. and Turner, L., 2017. Stem cells in court: historical trends in US legal cases related to stem cells. Regenerative medicine, 12(4), pp.419-430.

into a patent-eligible application of such a law." In other words, the court stated that the naturally produced elements and the therapeutic processes did not have a significant enough distinction to be patent eligible[29].

This decision was controversial as it rendered diagnostic patents that were already issued a threat of obsolescence[30]. Despite the controversy that the *Mayo v. Prometheus* case accompanies, the case was important for hESC cell inventions for a major reason. This case showed that the United States patent framework does not allow for simple deviations from the laws of nature. In essence, this means that hESC cell inventions must be able to prove their human-made aspect through more than just an instructional guide of how to use "law of nature" elements, as was the case with Prometheus's patents.

2.2.4 Association for Molecular Pathology v. Myriad Genetics, Inc.

Another landmark example of the Supreme Court limiting the scope of 35 U.S.C. §101[31] was in the *Association for Molecular Pathology v. Myriad Genetics, Inc.* case (hereinafter "Myriad case"). Although the case does not directly relate to human embryonic stem cells, it is related to the patentability of DNA sequences. Myriad Genetics was an owner of several DNA sequence patents, which essentially was produced through separating the DNA from its surrounding genetic material.

The Supreme Court ruled that the mere separation of the DNA sequence from its surrounding genetic material does not constitute a change so significant that it would bring about patent eligibility. The isolation of a DNA sequence does not change the fact that it is still naturally occurring, thus it falls into the limitations to being patent eligible[32].

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[29] Aggarwal, S. and Chandra, A., 2021. An insight into patent landscape analysis of plant stem cells. World Patent Information, 65, p.102025. Chennai, Elsevier.
[30] Ouellette, S.B., 2019. Landscape of granted US patents in personalized diagnostics for oncology from 2014 to 2018. Expert Opinion on Therapeutic Patents, 29(3), pp.191-198. Routledge, Taylor & Francis.
[31] Roskams-Edris, D., Anderson-Redick, S., Illes, J. and Kiss, Z.H., 2019. Medical Methods Patents in Neuromodulation. Neuromodulation: Technology at the Neural Interface, 22(4), pp.398-402. Paris: Elsevier.
[32] Caulfield, T.A., 2003. From human genes to stem cells: new challenges for patent law?. New York: Elsevier.

The importance of this decision for hESC related inventions is crucial. As mentioned previously, the method of obtaining human embryonic stem cells comes from extracting pluripotent cells from a human blastocyst. Therefore the human embryonic stem cells obtained shall not be patent eligible on their own, at least with no further steps taken to ensure the deviation from the laws of nature. Although, as hESC cells themselves are not patentable in their simplest form, it seems quite clear that the use of hESC cells in order to further create inventions may still be patent eligible.

Due to the Myriad Case and Mayo v. Prometheus, the patent eligibility related to the use of stem cells in the United States has become more uncertain, as the extraction could still fall under the Law of Nature[33]. In view of the above, and in order to make the procedure of determining patent eligibility more simple in relation to the laws of nature, the Supreme Court released their guidance on the subject matter in 2014.

2.2.5 USPTO Myriad-Mayo Guidance

In order to more broadly address the patent eligibility of inventions that relate to the Laws of Nature, Natural phenomenons and other Natural products, the Supreme Court released their *Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena, & Natural Products*. This guidance is often referred to as the USPTO Myriad-Mayo Guidance, and will be referred to as such hereinafter.

This guidance was released in 2014 following the two landmark cases, however the applicability of the guidance extends far further than the subject matter of the cases. As the Myriad case solely dealt with the isolation of DNA sequences, the impact of the result has been extended to a broader scope through the guidance released by the Supreme Court.

[33] Palavecino, L.A., Rodrigues, C.R., Bello, M.L. and Vasconcellos, A.G., 2021. Inventive step assessment of top selling monoclonal antibodies in Brazil. *Expert opinion on therapeutic patents*, *31*(3), pp.193-202. Rio De Janeiro: Taylor & Francis.

The guidance essentially gives three steps to be used to analyse whether an invention is patent eligible or naturally occurring. These are:

1. *Is the claimed invention directed to one of the four statutory patent-eligible subject matter categories: process, machine, manufacture, or composition of matter?*
2. *Does the claim recite or involve one or more judicial exceptions identified by the Supreme Court in Diehr (i.e., laws of nature, physical phenomena, or abstract ideas)?*
3. *Does the claim as a whole recite something significantly different than the judicial exceptions?*

The Myriad-Mayo Guidance is limited in scope to a selection of matters including importantly the following, *"(...) natural materials; nucleic acids; organisms; proteins and peptides; and other substances found in or derived from nature*". Although this does not specifically refer to stem cells or a more specific term indicating the use of them[34], the USPTO indicated that any further revised guidance would not be limited to the same scope as the Myriad-Mayo Guidance, and would include any natural product. Therefore, in 2019 the USPTO released their revised guidance on these matters.

Prior to the release of the USPTO revised guidance in 2019, the USPTO stated that the further guidance could include the ability to provide evidence on how the subject differs either functionally or in utility to the Laws of Nature, thus providing sufficient eligibility for a patent[35]. However, again, the revised guidance has no specific mention of stem cells either, meaning that the revised guidance has once again left uncertainty in the patentability of hESC related matters, especially in the patenting of the human embryonic stem cells themselves along with guidance for determining in which conditions this could be feasible.

[34] Cicka, D. and Quave, C., 2019. Bioprospecting for Pharmaceuticals: An Overview and Vision for Future Access and Benefit Sharing. Medicinal Plants, pp.17-34. New York: Springer.
[35] Sherkow, J.S. and Scott, C.T., 2015. Stem cell patents after the America Invents Act. *Cell stem cell*, *16*(5), pp.461-464. Cambridge: Elsevier.

3. Chapter 3: Human Embryonic Cell usage in COVID-19 Vaccines

This section aims to determine what hESC cell lines are used in the most widely available Covid-19 vaccines in the European Union and the United States of America. After the specific cell line is determined, it is beneficial to discuss the extent to which the hESC cells are used, as the level of usage may affect the patentability. This information has mainly been gathered through the study of *Innovations and development of Covid-19 vaccines: A patent review*[36].

3.1 Human Embryonic Stem Cell Lines

Human embryonic stem cells are derived from different variations of the original cell. These original cells are multiplied leading to situations in which our current hESC cell lines are derivatives of cells taken 50 years ago[37]. In this study, we will focus on two main hESC lines, the HEK-293 and the PER.C6 due to their prevalence in current regenerative medicines.

3.1.1 HEK-293 Context and Importance

HEK-293 is a hESC cell line originating from a human embryonic kidney cell. This line was collected by scientist Alex Van der Eb in the early 1970's at the University of Leiden. The exact origin of the aborted fetus cell is unknown due to the age of the cell[38].

This line of hESC cells is generally used for research in biotechnology and toxicology. The cells have also been widely used for testing purposes, such as efficacy testing and virucide testing[39].

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[36] Alshrari, A.S., Hudu, S.A., Imran, M., Asdaq, S.M.B., Ali, A.M. and Rabbani, S.I., 2021. Innovations and development of Covid-19 vaccines: A patent review. Journal of infection and public health. Chennai: Elsevier.

[37] Le Bail, R., Bonafina, A., Espuny-Camacho, I. and Nguyen, L., 2021. Learning about cell lineage, cellular diversity and evolution of the human brain through stem cell models. Current Opinion in Neurobiology, 66, pp.166-177. Amsterdam: Elsevier.

[38] Pulix, M., Lukashchuk, V., Smith, D.C. and Dickson, A.J., 2021. Molecular characterization of HEK293 cells as emerging versatile cell factories. Current Opinion in Biotechnology, 71, pp.18-24. Amsterdam: Elsevier.

[39] Zhu, G., Zhang, Y., Xu, H. and Jiang, C., 1998. Identification of endogenous outward currents in the human embryonic kidney (HEK 293) cell line. Journal of neuroscience methods, 81(1-2), pp.73-83.New York: Elsevier.

As will be discussed in a later chapter of this study, the virucide testing has become prevalent due to the SARS-CoV-2 outbreak.

3.1.2 PER.C6 Context and Importance

PER.C6 is a hESC line originating from a human retinal cell obtained from an aborted fetus in 1985. The cell line has proven to be useful especially in human adenovirus uses, making it an excellent tool for the development of vaccines[40]. Examples of vaccine research and development uses were related to diseases such as tuberculosis, malaria and HIV, with the current SARS-CoV-2 outbreak adding further uses as well.

3.2.1 BioNTech and Pfizer (HEK-293)

BioNtech and Pfizer combined their efforts to create the BNT162b2 Covid-19 Vaccine. For this vaccine, two patents were given, the US20190321458A1 and the US10729785B2. Within these patents, the use of HEK-293 was clear, however only for the testing phase of the vaccine[41]. The cell was used by BioNtech and Pfizer to recreate the specific conditions to determine whether their vaccine would be able to work effectively in the human body. Although the usage of the hESC cell line is not used in the vaccine itself, the testing phases of the vaccine would not be patent eligible in the European Union as shown in Chapter 2 of this study.

The BNT162b2 Covid-19 Vaccine uses messenger RNA (mRNA) which essentially teaches cells how to produce proteins that will cause an immune response in the human body[42]. The technology that BioNTech and Pfizer use for their vaccines does not require the use of human embryonic stem cells for any other purpose except the testing phase, which is why the use of

[40] Ghaderi, D., Zhang, M., Hurtado-Ziola, N. and Varki, A., 2012. Production platforms for biotherapeutic glycoproteins. Occurrence, impact, and challenges of non-human sialylation. Biotechnology and Genetic Engineering Reviews, 28(1), pp.147-176. Routledge: Taylor & Francis.
[41] Gasmi, A., Srinath, S., Dadar, M., Pivina, L., Menzel, A., Benahmed, A.G., Chirumbolo, S. and Bjørklund, G., 2022. A global survey in the developmental landscape of possible vaccination strategies for COVID-19. Clinical Immunology, p.108958. Amsterdam: Elsevier.
[42] Verbeke, R., Lentacker, I., De Smedt, S.C. and Dewitte, H., 2021. The dawn of mRNA vaccines: The COVID-19 case. Journal of Controlled Release, 333, pp.511-520. Amsterdam: Elsevier.

HEK-293 stem cells were chosen, as they have specific attributes that allow for the vaccine to be tested in an environment similar to the human body.

As of July 2020, BioNTech and Pfizer had 13 patents for their vaccine that were either accepted or pending. These were published in their financial statement[43] which showed that out of the 13 patents that had been applied for, ten were through the USPTO whilst only three were through the WIPO. This leaves a significant question as to the extent that the three WIPO patents cover a significant enough portion of the vaccine in order to be patent protected within the European Union as well. However, unfortunately the information in the WIPO patents is far too technical to fully understand without a deeper understanding of the field of research as well as the vaccines themselves.

3.2.2 Moderna (HEK-293)

Moderna has eight patents for their mRNA-1273 COVID-19 VACCINE in the United States. Out of these, three patents include the HEK-293 cell. The three are, US 10,898,574, US 10,703,789 and US 10,577,403[44]. Within these patents, the use of the HEK-293 cell line is quite prevalent as it details the use and benefits of using the line of cells. Through the use of this cell line, it becomes quite clear that the United States patent framework allows for the patenting of hESC related processes and inventions.

Through the patents listed above, the use of the HEK-293 hESC cell line is used solely for the testing of the mRNA-1273 Vaccine. The hESC cell is not present in the final version of the vaccine and therefore the cell is never transferred into the patients. However, as the cell is used in the testing phase of the process, the patents including the testing phases would not be patent eligible in the European Union, which is the reason why the application has been made in the United States.

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[43] "Certain of our technologies, including in particular certain proprietary manufacturing processes or technologies and/or neoantigen prediction technologies, are protected as trade secrets",.BioNTech SE, SEC Filing (July 21 2020), https://www.sec.gov/Archives/edgar/data/1776985/000119312520195911/d939702df1.htm.

[44] Li, Y., Tenchov, R., Smoot, J., Liu, C., Watkins, S. and Zhou, Q., 2021. A comprehensive review of the global efforts on COVID-19 vaccine development. ACS Central Science, 7(4), pp.512-533. Washington D.C.: ACS.

The Moderna vaccine uses the same mRNA technology as is used in the BioNTech and Pfizer vaccine, therefore the only hESC inclusive aspect of the development of the vaccine is in the testing phase. As the mRNA technology is ground-breaking due to its applicability to the development of many vaccines within a short period, as was done successfully with the Covid vaccine, protecting the technological know-how to its full extent is important for pharmaceutical companies.

In Moderna's quarterly report in 2020[45], Moderna stated that they had filed for 12 patents that were either accepted or pending. Out of these twelve, ten were filed through the USPTO and only two were filed through WIPO. Similarly to the case above, this difference may also leave Moderna in a situation in which the vaccine is not fully protected within the European Union. However, the complexity of the patents would require an expert in the field of medical or biotechnology research to determine exactly to which extent they would be unprotected within the EU. Interestingly, Moderna stated that they would not enforce their patent rights on those that produced their vaccine in order to combat the pandemic.

3.2.3 Janssen Pharmaceutica NV (PER.C6)

Janssen Pharmaceuticals created the Ad26.COV2-S Covid-19 vaccine. The difference in this vaccine to the previous two is that this vaccine is a human adenovirus type 26 (Ad26), whilst the other two are both Lipid-encapsulated mRNA vaccines[46]. Whilst the scientific difference of the two falls outside of the scope of this study, the importance in this differentiation is the use of hESC cells.

The Janssen vaccine contains a different cell lineage, the PER.C6 human embryonic stem cell. More importantly the process of producing the vaccine requires the hESC cell, as opposed to the

[45] Moderna, Quarterly Report, June 30, 2020 https://www.sec.gov/Archives/edgar/data/1682852/000168285220000017/mrna-20200630.htm
[46] Nikitina, I.B. and Smirnova, E.A., 2021. SARS-CoV-2 and Patent Activity. Molecular Genetics, Microbiology and Virology, 36(1), pp.10-14. New York: Springer.

previous two vaccines only requiring it for testing. The hESC cell is however removed in the final product, therefore it is also not transferred in any manner into the bodies of the vaccine recipients either. From an intellectual property point of view, this could create a differentiation in the patent eligibility of the vaccine as the criteria is different compared to the other two vaccines.

Despite this, Janssen has received two patents for the Ad26.COV2-S Covid-19 vaccine, the WO2021155323A1 and the CA3101131A1. This fact is significant for the study, as the patent is not registered by the USPTO or in the European Union. However, it shows that this usage is still patentable, although only in limited jurisdictions of the world.

As Janssen Pharmaceutica uses the PER.C6 human embryonic stem cell line throughout the production of the vaccine, the full patenting of the vaccine becomes more complicated. The PER.C6 stem cell line is especially useful for viruses that are difficult to cultivate, thus it is used to a much higher degree in comparison to the HEK-293 stem cell line[47]. Janssen Pharmaceutica uses a different technology to the mRNA vaccines previously discussed. This adenovirus vaccine technology works similarly to conventional vaccines, and the mass production of the vaccine utilises human embryonic stem cells to a comparatively greater scale.

3.3 International Patent Applicability

Through examining the patent technologies used in the examples provided previously, a clear difference in the levels of usage of human embryonic stem cells becomes apparent. As pharmaceutical companies are under pressure to patent the human embryonic stem cell inclusive patents outside of the European Union, the question arises in regards to what extent the vaccines are patent protected within the European Union.

[47] Ong-Lim, A.L., Shukarev, G., Trinidad-Aseron, M., Caparas-Yu, D., Greijer, A., Duchene, M., Scheper, G., van Paassen, V., Le Gars, M., Cahill, C.P. and Schuitemaker, H., 2022. Safety and immunogenicity of 3 formulations of a Sabin inactivated poliovirus vaccine produced on the PER. C6® cell line: A phase 2, double-blind, randomized, controlled study in infants vaccinated at 6, 10 and 14 weeks of age. Human Vaccines & Immunotherapeutics, pp.1-11. Routledge: Taylor & Francis.

Patents only hold their validity in the territory that they are granted in. For example, USPTO patents are only effective within the territory of the United States of America. As such, if inventors wish to gain full intellectual property rights on an international level, they must apply for the intellectual property protection in those specific territories as well. However when an invention requires steps that are patent ineligible in specific patent frameworks, the inventors are unable to patent those specific elements in that jurisdiction. This leaves parts of their inventions unprotected in those jurisdictions, causing some question as to which extent they can be used freely by competitors.

As the vaccine producers have opted to patent the hESC inclusive elements through USPTO patents, the question arises as to how effective these patents are within the European Union. In order to answer this, the Congress answered this question in their Patent Act under section 271 (g):

(g) Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer, if the importation, offer to sell, sale, or use of the product occurs during the term of such process patent. In an action for infringement of a process patent, no remedy may be granted for infringement on account of the non-commercial use or retail sale of a product unless there is no adequate remedy under this title for infringement on account of the importation or other use, offer to sell, or sale of that product. A product which is made by a patented process will, for purposes of this title, not be considered to be so made after–

(1) it is materially changed by subsequent processes; or
(2) it becomes a trivial and nonessential component of another product.

Congress added 271 (g) specifically in order to protect the pharmaceutical and biotechnological industries[48], hence its importance for human embryonic stem cells is noteworthy as well. Essentially, article 271 (g) considers a patent infringement to consist of the importation, use or

[48] Plomerl, A., 2010. Stem cell patents in a global economy: the legal challenges. Stanford Journal of Law Science and Policy, 3. California: Stanford University Press.

sale in the United States of any patented product regardless of where it was made. There have been multiple landmark cases regarding the article and the efficacy that it holds on international patent protection.

The major landmark case, *Eolas Technologies, Inc. v. Microsoft Corp.*, concerned Microsoft exporting part of a software from the United States which Eolas considered to be a violation of their patent. As such, the Federal Court examined whether this would constitute a patent violation under 271 (g). In summary, the court found that the exportation of part of the code by Microsoft could constitute a patent infringement under article 271 (g). In the SARS-CoV-2 vaccine context, this means that if an international pharmaceutical producer were to use the unpatented portions of the vaccines in their territory, the importation of materials, equipment or other elements used in the production of the vaccines could be seen by courts to constitute a patent infringement. However, under article 271 (g), case precedents have shown that the element which is being used, sold or imported should be physical in its nature. This was shown in the *Bayer AG v. Housey Pharmaceutical, Inc.* case, in which the Federal Circuit held that article 271 (g) concerned only physical patented manufacturing methods and not the gathering of information[49]. As such, the court held that Bayer's actions in identifying information did not infringe the patent rights of Housey Pharmaceutical. This precedent brings uncertainty to the extent to which United States patent rights can be used internationally, however it seems to allow for the transfer of information. Thus, in the SARS-CoV-2 vaccine context, as long as the elements that are being exported from the United States are not physical elements used in the manufacturing process, they would most likely not constitute a patent infringement.

In the case of human embryonic stem cells, the difference in patent frameworks has been identified clearly, as the European Union considered any use of hESC to be patent ineligible. Therefore, as all aspects of hESC cell line use in the vaccines are not patented within the European Union, this would leave those aspects unprotected and thus freely available for the use of by competitors. This may not be an issue for the first two examples that use the HEK-293 cell line for testing purposes, however Janssen Pharmaceutica are in a different situation in regards to

[49] Farnley, S., Morey-Nase, P. and Sternfeld, D., 2004. Biotechnology—a challenge to the patent system. Current Opinion in Biotechnology, 15(3), pp.254-257. New York: Elsevier.

protection within the European Union. As the PER.C6 stem cell line was used throughout the process of the vaccine as shown in section 3.2.3, Janssen Pharmaceutica has been unable to protect its inventions and processes by patenting all of those processes in the European Union. Although they have still received WIPO patents and other patents that would be applicable in the European Union, these do not include any of the processes including the human embryonic stem cell usage. As the vaccine has patent gaps within the European Union, these can be used by competitors in the European Union without violating the intellectual property rights of Janssen Pharmaceutica.

3.4. SARS-CoV-2 hESC Usage

Through determining the patents used in SARS-CoV-2 vaccines in section 3.2, it has become apparent that the extent to which the hESC cell lines have been used differs significantly. Each hESC cell line provides its own strengths and weaknesses for the research of and production of the vaccines. Incidentally though, the two of the main producers BioNTech and Pfizer as well as Moderna both found the HEK-293 cell line to be beneficial for their requirements. As the HEK-293 was only used for testing purposes, the extent to which they require patents including the human embryonic stem cell line seems quite limited. However, as Janssen Pharmaceutica used the PER.C6 hESC cell line for further purposes, the effect of successful patentability is far greater. As Janssen Pharmaceutica stated in their summary of AdVac and PER.C6 technologies, PER.C6 "*provides a manufacturing system for high-yield, faster and large-scale production of vaccines and monoclonal antibodies. It is especially useful for vaccine manufacturing that requires the production of hard-to-grow viruses"*[50].

Thus a clear distinction in the use arises due to the necessity of the extent that the human embryonic stem cells are required. As such, in the current patent frameworks in the United States of America and the European Union, a possibly unintended effect is caused. As Janssen

[50] JanssenMD® Professional Information Resource. 2022. AdVac® and PER.C6® Technology of the Janssen COVID-19 Vaccine. Available at: <https://www.janssenmd.com/janssen-covid19-vaccine/product-properties/product-technology/advac-and-perc6-technology-of-the-janssen-covid19-vaccine>.

Pharmaceutica requires more patents including hESC cell lines due to the extent of use throughout the vaccine's production, they have resorted to applying for patents outside of the European Union leaving a larger portion of their vaccine without patent protection within the there and in other jurisdictions. As they have applied for WIPO patents for the hESC non-inclusive segments, they still retain a certain level of patent protection on their vaccines in the European Union. However their patent protection level is far lower in comparison to those of BioNTech and Pfizer as well as Moderna.

In addition to this effect, another potentially unintended effect is caused as a result of the extent that the human embryonic stem cells are used. As Janssen Pharmaceutica's options to protect their patents have been limited in Europe, they have been forced to find alternative methods of protecting their hESC inclusive patents. In conjunction with the protection, they have also shifted a significant amount of their resources and general business activities outside of the European Union as well. The net result is that due to the more conservative approach in the European Union's human embryonic stem cell patent framework, pharmaceutical companies and their beneficiaries and stakeholders have preferred to shift their focus to markets that allow the intellectual property protection of their inventions and products more comprehensively. As SARS-CoV-2 vaccines do not require the full utilisation of human embryonic stem cells, a further potential future issue arises.

In the current state of medical advancements, human embryonic stem cells have not reached their theoretical potential[51]. As these advancements are likely in the very near future, potentially major future issues in the patent frameworks of both the United States of America and the European Union should be considered in order to have comprehensive coverage in place in advance. Human embryonic stem cells are only used in a relatively small portion of current products and inventions, however in the future once the technology has advanced, these cell lines may become the major elements or ingredients of products and inventions especially in regenerative treatments.

[51] Elisseeff, J.H., 2004. Embryonic stem cells: potential for more impact. Trends in biotechnology, 22(4), pp.155-156. Amsterdam: Elsevier.

One example of such likely future inventions is in the field of the treatment of Spinal Cord Injuries (also referred to as, "SCI"). The use of human embryonic stem cells has been seen as a very potential solution and may become a major element of a new path of treatment. As human embryonic stem cells are pluripotent in nature, their use in SCI could become the first regenerative cure to the injury that so far with conventional medical treatment is largely incurable. Researchers believe that the treatment will become a reality within a decade, as the human embryonic stem cells have shown "*remarkable results*"[52]. Thus, in the current patent frameworks of the European Union especially, the vast majority of patents required to achieve full intellectual property protection would be ineligible. Although this may be an intended effect in the patent framework of the European Union, it would lead to the further migration and concentration of companies developing regenerative medicines to the United States of America or other more liberal patent framework jurisdictions.

4. Chapter 4: COVID-19 Vaccine Patent Waivers

Due to the spread of the coronavirus (SARS-CoV-2) on a global level, there has been well-publicised shortage in the amount of vaccines supplied. This phenomena has been especially prevalent in developing countries where government budgets for medical spending are not sufficient to cover the vaccine cost for their citizens. Due to the patents and the protection of intellectual property secured by a few key companies, other international pharmaceutical manufacturers are unable to replicate the vaccines even though they have the technical capability of doing so[53].

In an attempt to off-set this shortage, there have been international pleas for the temporary waiver of patent rights on Covid-19 Vaccines. This temporary patent waiver would be focused on benefiting developing nations, as they have limited financial opportunities to obtain the vaccines. This shortage has pushed developing countries to purchase the cheapest alternatives which have

[52] Shao, A., Tu, S., Lu, J. and Zhang, J., 2019. Crosstalk between stem cell and spinal cord injury: pathophysiology and treatment strategies. Stem cell research & therapy, 10(1), pp.1-13. Singapore: Springer.
[53] Binagwaho, A., Mathewos, K. and Davis, S., 2021. Time for the ethical management of COVID-19 vaccines. The Lancet Global Health, 9(8), pp.e1169-e1171. Amsterdam: Elsevier.

shown far lower levels of efficacy, as shown in the study conducted on India's vaccine strategies [54]. The international call for a patent waiver was initiated by India and South Africa, who asked the WTO to push through a vote on a patent waiver for the vaccines. Following this, other WTO members also began to consider the possibility of a patent waiver on the matter. However, the main objections to the waiver came from nations that had competitively developed pharmaceutical industries and injected huge amounts of capital into the process.

The United States began its consideration of implementing a patent waiver on the subject matter in May of 2021, followed by the European Union's proposal in June of 2021. Unfortunately many discussion points related to the vaccine patent waivers are political in nature and therefore fall outside the scope of this study. This section will instead focus on the aspects that directly or indirectly affect the intellectual property right owners as well as presenting a comparative analysis on the potential implementation of the waiver between the United States and the European Union.

4.1 EU Communications

The European Union and its member states also began considering the possibility of a patent waiver or "TRIPS waiver" as it has been generally referred to. Due to the prevalence and influentiality of large pharmaceutical companies in the European Union, the early discussions were not successful in reaching a conclusion despite the well-known global vaccine shortage[55]. An example of such reluctance is from Germany, where there are clear indications of interests to protect BioNTech, their leading pharmaceutical company which has gained a significant global position.

[54] Foy, B.H., Wahl, B., Mehta, K., Shet, A., Menon, G.I. and Britto, C., 2021. Comparing COVID-19 vaccine allocation strategies in India: A mathematical modelling study. International Journal of Infectious Diseases, 103, pp.431-438. New Delhi: Elsevier.

[55] Zhou, Y.R., 2022. Vaccine nationalism: contested relationships between COVID-19 and globalization. Globalizations, 19(3), pp.450-465. Oxfordshire: Taylor & Francis.

As the European Union does not wish to grant a full patent waiver as suggested by the WTO, they have instead given their feedback to the WTO whereby suggesting alternate methods to combat the vaccine shortage in a different manner.

First, the TRIPS agreement ensures certain exceptions that would allow WTO members to have access to medicines. The 2001 WTO Doha Declaration on the TRIPS agreement specifies that developing nations would not be obligated to implement the TRIPS agreement until July 2021. As this date has already passed (including the date of the EU communications to the WTO), the EU stated that this date should be extended until 2033[56]. This would allow time for developing countries to offset the shortage of vaccines whilst also potentially developing their own pharmaceutical infrastructures.

There are three methods of combating the shortage in vaccines that the European Union considered: voluntary licensing, compulsory licensing and waiving IP rights. Voluntary licensing is the agreement, in this case, between the vaccine developer and international producers. This partnership would allow developers to use the specific know-how to produce the vaccines whilst usually paying the applicable licence fees. Compulsory licensing is the government granted licensing without the consent of the intellectual property right holder. This may also include certain remunerations for the intellectual property right holder. Lastly, the patent waiver would remove all intellectual property rights allowing for the free production and use of the know-how, usually without any remuneration to the intellectual property right holder.[57]

The TRIPS agreement and the Doha Declaration would specifically allow for a compulsory licensing method, which the European Union believes could be the solution to the shortage in vaccines. This was most likely chosen as it is the medium option in terms of balancing the benefits of both the intellectual property right owners and the developing nations in need of their vaccines.

[56] Mercurio, B., 2021. The IP Waiver for COVID-19: bad policy, bad precedent. IIC-International Review of Intellectual Property and Competition Law, 52(8), pp.983-988. New York: Springer.
[57] Urias, E. and Ramani, S.V., 2020. Access to medicines after TRIPS: Is compulsory licensing an effective mechanism to lower drug prices? A review of the existing evidence. Journal of International Business Policy, 3(4), pp.367-384. New York: Springer.

4.2 US Communications

In May of 2021, the United States stated that they would support the patent waiver that was suggested by India and South Africa. This meant that the US was open to discuss the details of how the patent waiver should be implemented. However, despite this, there has been no progress in agreeing to support the patent waiver. In fact the US has not openly supported any text nor revised text that has been submitted to the WTO[58].

Therefore, the decision to support the patent waiver has had only limited political effects, and no legally binding agreements have been reached. The support has generally pressured other non-supporters to reconsider their stance on the matter, however the text-based discussions have not achieved the goals that India and South Africa were attempting to obtain.

4.3 Further Implications of the Patent Waiver

The TRIPS waiver has been largely a political discussion rather than a legal discussion on a global scale. The discussion has yet to achieve any outcome, however certain legal aspects have arisen from the situation.

Depending on the type of waiver of rights, there are different legal implications for all parties involved. When considering the compulsory licensing and patent waiver options, there are multiple material and non-material exchanges that are necessary to achieve the goals of the TRIPS agreement. First, in this case, the transfer of the know-how will not suffice due to the technical difficulty of producing vaccines. In order to reproduce the vaccines, external producers will require the equipment, specific biotechnological supplies and appropriate training. Therefore many questions arise as to how the TRIPS waiver will address these transfers comprehensively.

[58] Storz, U., 2021. The patent maze of COVID 19 vaccines. Expert opinion on therapeutic patents, 31(12), pp.1177-1188. Routledge: Taylor & Francis.

The major successful model that has been the aim for the TRIPS waiver has been the AIDS/HIV pandemic. In 1996, the pandemic of AIDS/HIV brought about an international agreement on a patent waiver which resulted in the prices of the treatment to drop by 99.9%[59]. As a result, the fatality rates from the AIDS/HIV pandemic were greatly lowered, even in developing countries that initially couldn't afford the treatment. Therefore, in view of the above success, the international community has been promoting the TRIPS waiver with the same approach. Although the SARS-CoV-2 pandemic has become less problematic in countries with access to the vaccines, developing countries like India and South Africa have been unable to control the pandemic in the same manner and a quick resolve is required.

4.4 hESC Discussion

As these patents have been shown to include human embryonic stem cells, will this further complicate the TRIPS waiver process? There is an important discussion to be held on an international level on the validity of these patents as they are not patent eligible on a global scale. For each vaccine, the pharmaceutical companies have filed multiple patents, of which only a handful include the hESC related matters. These patents are only attainable in certain jurisdictions which creates the discussion of the need to waive these patents specifically, as they would not be patent eligible in their respective jurisdiction. For example when the pharmaceutical companies have filed patents in the United States for the hESC inclusive inventions, the patents only hold validity in the territory of the United States. These patents may have only limited effects in the international context.

To combat this fact, the Covid-19 vaccine producers have opted to file for their patents internationally, as not all of their patents include hESC lines and are therefore patent eligible even within the European Union. However, for example with Moderna, their three patents that include the HEK-293 cell line would not be patent eligible in many jurisdictions, hence the patent application in the United States. Therefore, pharmaceutical producers could in theory use

[59] D'Angelo, A.B., Grov, C., Johnson, J. and Freudenberg, N., 2021. Breaking Bad Patents: Learning from HIV/AIDS to make COVID-19 treatments accessible. Global Public Health, 16(10), pp.1523-1536. Routledge: Taylor & Francis.

the patented material from the three hESC inclusive patents freely if they do not plan to directly or indirectly operate in the territory of the United States. However, as they have other patents internationally for the vaccine that do not include the hESC lines, a full copy of their vaccine would infringe their intellectual property rights in regard to other matters and patents.

For Janssen Pharmaceutica's Ad26.COV2-S Covid-19 vaccine, a more interesting precedent is set for the international community. As their vaccine contains the PER.C6 hESC cell line throughout the production process, the vaccines would be patent ineligible within the European Union and other jurisdictions that do not allow for the patenting of hESC related inventions. Thus, the vaccine patents should fall outside of the scope of the TRIPS waiver. However, Janssen Pharmaceutica's vaccine patents have also been protected through the WIPO, which would cover at least those sections of the vaccine in all WIPO member states, including the European Union.

In summary, the TRIPS waiver has created an interesting dilemma within the jurisdictional patent frameworks, as the call to temporarily waive the SARS-CoV-2 vaccine patents is partially unnecessary. However, as pharmaceutical companies have sought full intellectual property protection for their inventions, the patent waiver would be needed in order to fully replicate the vaccines in developing countries that lack the current supply of the vaccines.

4.5 Alternative Solutions

An alternative approach to the TRIPS waiver issue has been considered in academic circles, which aims at dealing with future pandemics and emergency situations in a manner that would resolve the necessity for future patent waivers. According to this approach, a direct governmental support program would need to be established in cases of pandemics or emergency situations that require the development of an invention or product[60]. The belief is that intellectual property rights and emergency situations are in conflict at the point in which intellectual property rights block the ability to properly address and resolve emergency situations. As intellectual property

[60] Lindsey, B. (2021, June 3). Why intellectual property and pandemics don't mix. Brookings. https://www.brookings.edu/blog/up-front/2021/06/03/why-intellectual-property-and-pandemics-dont-mix/

rights, especially with patents, block the short term use of production capacities of all producers, including those of competitors, emergency situations cannot be properly handled with the interests of societal benefits. As an option, the author believes that a direct public governmental support program would resolve the issue. In this approach, governments would provide direct support to the appropriate organisations, for example pharmaceutical companies with a solution, whether medication or a vaccine to the SARS-CoV-2 outbreak, which would cover the research and development costs of the invention or product. Furthermore, an agreement would be made in which further financial benefits would be made to incentivise the rapid development and future cooperation as well. This would essentially grant the government full access to use and distribute the invention as if no patent existed.

For human embryonic stem cells, this could potentially incentivise pharmaceutical companies and their beneficiaries to enjoy the financial aspects of a patent whilst the general public would enjoy the benefits of easier access to the invention. In the European Union, this would potentially result in the lack of necessity for patent eligibility of human embryonic stem cells, as pharmaceutical companies would enjoy the benefits of inventing without the need for intellectual property rights. As this method of approaching emergency situations is purely theoretical and to date also unproven, it is difficult to examine the exact effects that this would have on human embryonic stem cell research. However the theory suggests an outcome that would balance the rights of all parties equally and in a beneficial manner for the greater good of society[61].

Due to the vast potential in the future for human embryonic stem cell research, pharmaceutical companies may approach this direct support method hesitantly, as the benefits of intellectual property rights may outweigh the short term financial rewards. Unintended discoveries during the research and development phase may be worth far more financially and strategically than the initial agreement would account for, hence pharmaceuticals would for the most part side with the conventional approach of seeking full intellectual property rights instead. However, the caveat to the direct support program is the promise of financial reward regardless of successful invention, which would remove the risk of investing large amounts into research and development that do

[61] Emanuel, E.J., Buchanan, A., Chan, S.Y., Fabre, C., Halliday, D., Heath, J., Herzog, L., Leland, R.J., McCoy, M.S., Norheim, O.F. and Saenz, C., 2021. What are the obligations of pharmaceutical companies in a global health emergency?. The Lancet, 398(10304), pp.1015-1020.

not lead in the development of the initially intended result. The lower risk would justify the lower reward, hence it could well be accepted as an appropriate compromise by some companies who are more accustomed to a high risk environment.

5. Chapter 5: Comparison of EU and US hESC Patent Frameworks

Through the research and discussion in this study, the similarities and differences between the two legal frameworks has become apparent in relation to the patentability of hESC related subjects. In general, it can be summarised that the European Union patent framework is more driven by the ethical and moral justifications, especially through the limitations set through the Biotechnology Directive on “ordre public” and “morality”. This has resulted in the lack of patent eligibility for human embryonic stem cells and their derivatives, as the fertilisation of an ovum is considered as resulting in the automatic status of a human embryo.

In the United States, the patent eligibility of human embryonic stem cells has been granted for over two decades. Although the framework has changed over this period of time, in general there is still the opportunity to seek patent protection for hESC related subjects. There are certain limitations and criteria that must be fulfilled in order to attain this protection, however it has created a significant opportunity for hESC researchers to protect their work. As a result, pharmaceutical companies and their investors have shifted their operations to the United States in order to receive full intellectual property protection from the patent framework provided there. This is especially significant for the human embryonic stem cell patents as shown in Chapter 3 of this study, as all SARS-CoV-2 vaccines that include the HEK-293 human embryonic stem cell line have patented their hESC inclusive patents in the United States. This is also illustrated by the the significantly greater total pharmaceutical market size of the United States in comparison with the European Union, which can be partly attributed to the allowance for human embryonic stem cell inventions receiving patent eligibility.

One of the main effects of this framework difference has been the industry protecting their research and inventions in the United States through patents, as shown in Chapter 3. For

example, Moderna has received three patents which include the human embryonic stem cell derivative line HEK-293, the use of which would qualify the patent ineligible in the European Union due to the use of the human embryonic stem cell line. Although the hESC lines used in the Moderna and BioNtech Pfizer vaccines are only used for the testing portion of the production, this would not be patent eligible in the European Union patent framework as shown through their use of USPTO patents. The interesting example comes in the Janssen Pharmeceutica vaccine, as this vaccine uses the PER.C6 hESC cell line throughout the production of the vaccine. Although the hESC cells are removed before the final product, this difference is considerable. This is also apparent through the use of alternate patents to the previous two examples, however as they did not apply for patents through USPTO it is difficult to determine whether this vaccine would have received a patent under the United States patent framework.

Due to the apparent differences in patent frameworks, it has become clear that the extent to which human embryonic stem cells are used negatively affects the intellectual property rights that can be obtained in order to fully protect the invention. As shown in the SARS-CoV-2 vaccine example, as Janssen Pharmaceutica uses human embryonic stem cells to a further extent for the mRNA vaccines[62], they can not patent a greater portion of their invention in the European Union. In this example, Janssen is still able to protect a significant amount of their vaccine even within the European Union as not all aspects of the production include the stem cell lines. Future products or inventions that are more reliant on human embryonic stem cell usage may not be able to be protected with patents within the European Union. This has become clear within the ongoing development of future potential regenerative medicines, especially in spinal cord injuries. As currently researchers believe that the use of human embryonic stem cells has the potential to become the breakthrough tool in providing spinal cord injury treatments, these medicines may require the usage of human embryonic stem cells throughout the production of the invention. Therefore, these inventions would not be able to receive even limited amounts of patent protection within the European Union. Furthermore, as USPTO patents were shown to have uncertain levels of protection on an international scale, these would not aid in the protection of their inventions within the European Union itself.

[62] Cao, M., Su, X. and Jiang, S., 2021. Broad-spectrum anti-coronavirus vaccines and therapeutics to combat the current COVID-19 pandemic and future coronavirus disease outbreaks. Stem Cell Reports, 16(3), pp.398-411. Beijing: Elsevier.

The United States has become a destination for protecting patents that include hESC related inventions[63]. This has been especially apparent with the SARS-CoV-2 vaccines, as the pharmaceutical companies have opted to protect their inventions in that patent framework. This difference in the patent framework between the European Union and the United States of America has resulted in many different results. Mainly, for pharmaceutical companies and their investors, a large portion of their business activities is now conducted in the United States where they are able to enjoy the benefits of patent protection not attainable in the European Union. As shown through the study conducted by The European Federation of Pharmaceutical Industries and Associations, in the period of 2013 through 2018, new medicines launched in the US market accounted for 65.2% of the global market whilst new medicines launched in the EU market accounted for only 17.7% of the global market[64]. This difference cannot be fully attributed to the patent framework on hESC related inventions, however it shows the general trend of the differences in European Union and United States legal frameworks on the intellectual property of emerging medical inventions.

One of the major differences arising from this study is in the definition of a human embryo. In the European Union, upon the fertilisation of an embryo, the embryo is defined as a human embryo thus gaining certain rights and limitations. In essence, the European Union has determined through its legislation that human life begins at the moment of fertilisation. However, in the United States, a 14 day rule is applicable instead. This means that upon the fertilisation of the egg, there is a period of fourteen days before the embryo is considered a human embryo. Therefore, this allows for the use of the embryo for that period of time as it is considered to not have developed in a manner that would constitute gaining the full rights and limitations of a human at that point. Although the changing of this definition would be an ethical and moral discussion, this definition difference has resulted in the ability to patent human related matters in the United States whilst they are not patent eligible in the European Union.

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[63] Pimenta, C., Bettiol, V., Alencar-Silva, T., Franco, O.L., Pogue, R., Carvalho, J.L. and Felipe, M.S.S., 2021. Advanced Therapies and Regulatory Framework in Different Areas of the Globe: Past, Present, and Future. Clinical Therapeutics, 43(5), pp.e103-e138. New York: Elsevier.

[64] 2019. The Pharmaceutical Industry in Figures. Available at: <https://efpia.eu/media/413006/the-pharmaceutical-industry-in-figures.pdf>. EFPIA

Another key difference between the European Union and the United States is in the patentability of inventions that are naturally occurring. In the United States, the Myriad decision by the Supreme Court essentially made naturally occurring inventions patent ineligible. In order to become patent eligible in the United States, there must be proof of a derivation to laws of nature. However, this aspect of the patent framework on human embryonic stem cells is quite evident between the two jurisdictions, as under the Biotechnology Directive in the European Union, naturally occurring inventions can still be patentable. In order to have a patent eligible naturally occurring product or invention in the European Union, the product or invention must be isolated from its natural environment or it must be produced by a non-natural process. Although human embryonic stem cells and their use make products and inventions patent ineligible in the European Union, this aspect of the patent framework would allow for naturally occurring products and inventions which the United States currently do not allow for.

For the patent waiver, there is a difference in approach between the frameworks analysed here. Although the reasons for the approach that the United States have taken come mainly from a political standpoint, it is note-worthy that they have decided to approach the TRIPS waiver by providing it full support. As a large portion of the intellectual property rights surrounding the SARS-CoV-2 vaccines are in the United States, waiving these patents, albeit temporarily, could have a significant effect on the outlook of the patent framework from pharmaceutical companies and their investors. The European Union on the other hand has taken a more systematic approach in finding a medium between the rights of the pharmaceutical companies and the greater public good, the needs of international nations that lack the capability to obtain the vaccines. The approach of supporting a compulsory licensing system would benefit both sides accordingly. Although the European Union may have no need to support the hESC related patents, pharmaceutical companies like Pfizer are still based in the European Union and hold several patents that do not include hESC lines in their vaccine patents. Therefore it may be in the EU's best interest to continue to support the approach that they have currently been promoting related to the TRIPS waiver.

5.1 Suggestions for hESC Patent Framework Improvements

The current differences in the human embryonic stem cell patent framework between the United States of America and the European Union are quite substantial. These create unequal rights for multiple stakeholders ranging from investors, pharmaceutical companies, citizens to their governments, calling for a discussion on what changes should be implemented in order to balance these rights. The discussion should be approached from two perspectives, the national jurisdiction as well as the international jurisdictional perspectives.

The suggested improvements in this section will be based on the comparison between the two patent jurisdictions. They shall be based on the comparison and analysis conducted which has determined the strengths and weaknesses of both frameworks. Therefore, if one jurisdiction has a legislative weakness, in terms of the patentability of hESC related matters, the other jurisdictional view will be considered as a basis to determine if the patent framework could be strengthened.

5.1.1 EU Patent Framework Improvements

From a European Union perspective, the current patent framework creates a strong incentive for investors to transfer their operations to the United States or other frameworks that allow for the patenting of human embryonic stem cell related inventions. As the patenting of hESC related matters is strictly prohibited, there should be a reconsideration for reform in this specific field of research. This section will be based on the assumption that the European Union is willing to reform their patent framework, as the current discussion on reform is largely political, moral and ethical in nature, and thus it falls outside of the scope of this study.

Firstly, a redefinition of the human embryo is suggested[65]. The instant an egg is fertilised it obtains the human embryo status within the European Union. In order to allow for a larger

[65] Oliveira, R.A.D. and Fierro, I.M., 2018. New strategies for patenting biological medicines used in rheumatoid arthritis treatment. Expert opinion on therapeutic patents, 28(8), Taylor & Francis, pp.635-646.

patentability scope, the definition should give a more flexible time frame for patent eligibility. This could be done through redefining the human embryo to a later stage in the development of the embryo, for example similarly with the United States framework. The attempt to adopt this method, however, might lead to and be obstructed by a major moral debate as the change in definition would indirectly define when human life is legally considered to begin.

Another option for the European Union would be to allow for the patentability of hESC related inventions, if and only if specific hESC lines are used. This exception could be added in order to allow for the use of, for example, HEK-293 and PER.C6 cell lines which have been collected several decades prior and are infinitely reproducible. This would allow for stem cell research to be patent eligible and create incentives for multiple related parties. However, this option could create an exception that could be too specific in the long-run. As this would only allow specific cell lines to be used, these cell lines would have to be chosen in a specific manner to avoid benefiting or harming certain cell lines. Therefore, a more realistic approach would be to allow patent eligibility for human embryonic stem cells that have been collected, extracted and multiplied before a certain date. The clarification would therefore be based on time instead of a specific procedure of picking appropriate human embryonic stem cell lines. This option does not avoid all moral discussions, however should create far less debate as the cell lines do not and can not harm any further human embryos[66].

Lastly, the European Union could implement an exception to the extent that human embryonic stem cells are used in order to receive patent eligibility. This could be done through applying an exception in which inventions that do not include the application of human embryonic stem cells in any form or stage should be patent eligible. For example, in the case of BioNTech and Pfizer as well as Moderna, their use of the HEK-293 hESC lines would be patent eligible as they are only used in the testing phases. The testing phase of the product should not determine patent ineligibility on its own, as this is only done in order to prove the effectiveness of the product on humans. This stage could be, and has been done using non-human stem cells, however for full reliability and assuredness hESC cells were used to show the effect on humans. This could prove

[66] Cornelissen, M., Małyska, A., Nanda, A.K., Lankhorst, R.K., Parry, M.A., Saltenis, V.R., Pribil, M., Nacry, P., Inzé, D. and Baekelandt, A., 2020. Biotechnology for tomorrow's world: scenarios to guide directions for future innovation. Trends in Biotechnology, Elsevier, pp. 434-444.

to be a useful exception, as the human embryonic stem cells would not at any point have been directly used in the production of the invention.

5.1.2 US Patent Framework Improvements

As the United States of America has generally accepted the use of human embryonic stem cells to be patent eligible, they have created a large incentive for both pharmaceutical companies and investors to operate in their jurisdiction.

However, currently there is some ambiguity as to the extent that human embryonic stem cells can be used, as shown in chapter 2.2. As mentioned in chapter 2.2.5, currently the ambiguity stems from the lack of reference to human embryonic stem cells specifically. Therefore, the USPTO should address hESC cells specifically in a manner that clearly defines to what extent they can be used and in which manner. More specifically, a clear judgement on whether human embryonic stem cells on their own can be patented. Due to the Laws of Nature exceptions, these would most likely fall outside of the patent eligibility scope. However, the use of these in order to create inventions should be exempt as they are used as a tool in order to create something that is not naturally occurring.

As shown in the *Association for Molecular Pathology v. Myriad Genetics, Inc.* case, patent eligibility must prove a distinction from the laws of nature. As there is no specific mention of human embryonic stem cells in any United States patent legislation, this leaves uncertainty as to what extent human embryonic stem cells must be changed in order to constitute a distinction from the laws of nature. Human embryonic stem cells are, in their purest form, naturally occurring which leaves doubt as to their patentability. However, the patenting of human embryonic stem cells themselves is often unnecessary as commonly hESC cell lines are only used in order to aid in the production or testing of an invention. Nonetheless, due to this uncertainty, the United States could adopt human embryonic stem cell specific provisions in order to provide clarity on the situation.

In order to clarify the guidelines, the USPTO stated that further clarification on the matter would be provided through revised guidelines on the matter. In 2019 the USPTO released a revised guidance relating to the laws of nature and its patentability. However, as previously mentioned, the guidance did not specifically refer to human embryonic stem cells or any of the elements related to hESC. Thus, the USPTO may wish to provide further guidelines on specific matters related to hESC, as the current patent framework may negatively affect the interests of pharmaceuticals and their investors.

In order to provide clarity on the issue of human embryonic stem cells being naturally occurring and the evident unclarity resulting from not fulfilling a distinction from the laws of nature as shown in the Myriad decision, the United States could adopt a similar approach to the European Union and the Biotechnology Directive. In the Biotechnology Directive, exceptions have been listed in order to allow for the patent eligibility of naturally occurring inventions or products. Thus, the United States could adopt similar exceptions in their patent framework in order to clearly distinguish how naturally occurring inventions or products could still be patent eligible. Mainly, the exceptions of isolating the naturally occurring aspect from its natural environment, or proving that the product or invention was obtained through an unnatural process.

As human embryonic stem cell research has reached a point in which the clear benefits of their use for the common good of society is apparent, there is need for further USPTO guidance on their specific and exact use in order to maintain the current incentives that the United States has intended to create with their existing patent framework. Furthermore, there is need for clarification in the Patent Act, specifically in article 271 (g). As the article was added by the Congress in order to protect biotechnology and pharmaceutical companies on an international level, there could be benefits in clarifying the article's intention. As shown in the cases, *Eolas Technologies, Inc. v. Microsoft Corp.* and *Bayer AG v. Housey Pharmaceutical, Inc.*, the article is being interpreted in a manner that would not benefit the protection of human embryonic stem cell research and biotechnology research either. The outcomes from the cases show that if the elements that are used in the patent protected production are physical, then they shall be considered to violate the patent rights. However, if the elements being exported, used or sold are non-physical then they shall not constitute a violation of the patent rights. As biotechnology, and

human embryonic stem cells specifically, require a large amount of information transfer, for example guidelines and instructions, these would not be considered to be protected under article 271 (g) of the Patent Act. Therefore, the United States could consider clarifying the intention of the article by clarifying which elements should constitute a breach of patent protection. This could be done through the implementation of including information transfer, sale or use as well, due to the extent that these are used in human embryonic stem cell research.

5.1.3 Patent Framework Improvements on Future Technologies

SARS-CoV-2 vaccines have shown different levels of reliance on human embryonic stem cells. In the process of attempting to protect their intellectual property, some companies have confronted several difficulties. As shown previously, the effect of the current patent framework has not severely affected the intellectual property rights of BioNTech and Pfizer as well as Moderna, as they only require hESC cell lines for the testing phases of their vaccines. As such, the patents requiring the use of the HEK-293 stem cell lines used are limited and therefore still almost fully protected even within the European Union which considers any use of hESC cell lines to be patent ineligible.

However, as the inventions become more reliant on the use of human embryonic stem cell lines, such as in the case of Janssen Pharmaceutica, the intellectual property rights greatly diminish on an international level. As Janssen Pharmaceutica are reliant on the PER.C6 stem cell line throughout the production of their vaccine, they have attempted to apply for patent protection in jurisdictions that allow for the use of human embryonic stem cells.

Similar issues would therefore also be faced in attempts to protect new future technologies that are more or fully reliant on the use of human embryonic stem cells. With developing technologies creating the potential to use hESC to its full extent, the patent framework of the European Union especially will be tested as they will be fully patent ineligible in the current framework. Therefore, there is a potential need for a patent framework reform in the human embryonic stem cell field specifically. Without a reform, the market gap between the European

Union and the United States in the medical field will continue to grow, pushing European pharmaceuticals to shift their operations into the US market.

There are several steps that can be taken to potentially improve the patent framework in order to be equipped for the future technological advancements. First, the European Union could redefine the Human Embryo in order to allow for a period of time in which research and the products thereof would constitute patent eligibility. A redefinition could be done through allowing a period of time in which the fertilised egg is considered to be developing, after which it would be considered a human embryo, similar to the United States framework. Furthermore, the European Union could consider allowing the patentability of human embryonic stem cell lines that are chosen based on certain criteria. Such criteria could include specifications of the date obtained, the manner in which the human embryo became available and provision of hESC cell lines that are made available without any commercial financial gain. A list of criteria would be required in order to allow for the use of several stem cell lines to be patent eligible, as different stem cell lines bring upon different uses[67] as demonstrated through the comparison of the HEK-293 and PER.C6 stem cell lines.

The United States should also reconsider certain elements of their human embryonic stem cell patent framework in order to become further equipped for future advancements in the field of research. Currently, the limitations regarding the patent ineligibility stemming from the laws of nature cause uncertainty as to the extent to which human embryonic stem cells can be patent protected in the United States. Thus, a potential improvement would be to adopt a similar approach to the European Union in this regard. This could be potentially achieved through adding exceptions to the laws of nature. Exceptions such as removing the naturally occurring element from its natural environment, as well as obtaining the naturally occurring element through unnatural means may create certainty as to the extent that human embryonic stem cells can be patented as well as used in inventions that seek patent eligibility.

[67] Kong, M. and Zhou, D., 2021. Establishment of universal human embryonic stem cell lines. Immunology Letters, 230, pp.59-62. Amsterdam: Elsevier

CONCLUSION

New technologies have been increasing the rate of developing inventions especially in the medical field. Often new technologies pose difficulties for legal frameworks, which is shown in the case of human embryonic stem cell research and its protection. Human embryonic stem cells have proven to be valuable tools in the development of medicine, with the potential to change the limits of modern day medicine. However, as they are obtained through the destruction of a human embryo, they pose different legal, moral and ethical problems. In the study, a comparative analysis on the European Union and United States of America patent frameworks was conducted in order to determine the strengths and weaknesses. The goal of the study was to determine the strengths and weaknesses in order to suggest potential improvements to both legal frameworks.

First, the European Union patent framework on human embryonic stem cells was conducted in order to determine how hESC cells affect the patentability of inventions that included them. In summary, the European Union considers any invention that includes human embryonic stem cells to any extent patent ineligible. This is mainly due to the human embryo gaining full human status upon the fertilisation of the egg, therefore as the use of human embryos is not patent eligible there can be no use of them within the patent application.

The United States patent framework on human embryonic stem cells differs in its approach, as the human embryo is defined differently. In the United States, there is a fourteen day period from the fertilisation of the egg and when it is considered a human embryo. Therefore, this period of time allows for the collection of human embryonic stem cells and their use in a patentable manner. However, there is still some uncertainty on the patentability of innovations that use human embryonic stem cells, as the extent is not currently defined.

In order to more clearly show the difference between the two frameworks, the use of SARS-CoV-2 vaccines was used as an example. The vaccines chosen all used different variants of human embryonic stem cell lines, the HEK-293 and PER.C6. The two stem cell lines were used to different extents in the three chosen vaccines, from the testing phase to the actual

production of the vaccines. The study found that for the vaccines that used HEK-293 stem cell lines in their testing, patents were issued by the United States Patent and Trademark Office. This example shows the clear difference between the two frameworks as European Union based pharmaceutical companies (for example Pfizer) applied for patent protection on the human embryonic stem cell inclusive segments in the United States.

As these human embryonic stem cell inclusive SARS-CoV-2 patents were granted in the United States by the USPTO, the rights extend throughout the territory of the United States only. Therefore, with the TRIPS patent waiver discussions that were started in 2020 by South Africa and India, there have been discussions between the WTO, the European Union and the United States of America as to how this could be done. There has been no conclusion to the talks as of the date of this study, however certain issues have arisen from the TRIPS waiver in relation to human embryonic stem cell inclusive patents. As the hESC inclusive patents only hold validity in the United States, theoretically these could be used without the need of the TRIPS waiver, as long as the pharmaceutical producer using them is not using them in direct or indirect business with the United States. However, realistically the SARS-CoV-2 vaccine patent holders have covered their rights by applying for international patents on the non-hESC inclusive sections, therefore using the USPTO patents would most likely not allow for the full adoption of the technology to create the vaccine.

Through the analysis of the strengths and weaknesses of the two chosen patent frameworks, the two were compared in order to determine some potential improvements. As the study aims to give concrete and proven improvements, the strengths of one jurisdiction were used as a basis for suggesting improvement tools for the other. For example, the definition of the human embryo is vastly different between the European Union and the United States. As pharmaceuticals and their investors are moving their business operations to the United States to seek patent protection for their innovations, the European Union may consider broadening the scope of their patent protection on human embryonic stem cell inclusive inventions. To do this, the European Union could reconsider the definition of the human embryo by using a similar approach to the United States.

In conclusion, the current human embryonic stem cell patent framework in the European Union has created an effect in which pharmaceutical companies and their investors move their operations to the United States in order to fully protect their intellectual property and ensure that the high research and development costs spent on their inventions is not lost. Whether this effect is directly caused by the framework, and whether it is intended or unintended, the United States medical industry has released almost four times more new medication between 2013-2018 as shown in chapter 5 of this study. There is currently a large gap between the two markets, and although the difference in hESC patent frameworks is not fully accountable, the market gap will only continue to grow as a result of the likely continuing and expanding development of human embryonic stem cell research.

The scope of this study has been limited specifically to the patentability of human embryonic stem cell research and its use in inventions. As such, further studies on the topic may be required to give a full in-depth understanding of the topic for the purposes of strengthening hESC related patent frameworks. As the most commonly used human embryonic stem cell lines are decades old in their origin, there is a lack of clarity as to how they were specifically obtained. The topic of human embryonic stem cells is widely considered to be controversial, however a study into the origin of the cell lines could prove to be beneficial in terms of their controversy. As the European Patent Office clarified their stance through article Article 53(a) EPC, further study on the origin of the cell lines should be conducted in order to change the conventionally-accepted standards on human embryonic stem cells.

The utilisation of hESC in research has shown great potential for the greater good of society, therefore it deserves the increasing amount of capital injected into research in this field in the last few decades. However, as this paper has shown, the complicated inherent moral and value issues related to the utilisation of embryos to draw stem cells has prevented the full protection of intellectual property rights. There is a need for the regulations to be mutually clarified and set globally to achieve a balance between the interests of stakeholders and the principles of morality and human values.

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