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Matthews, Duncan ; Brown, Abbe; Gambini, Emanuela ; McMahon, Aisling ; Minssen, Timo; Nordberg, Ana; Sherkow, Jacob S. ; Wested, Jakob; Van Zimmeren, Esther

2021

Document Version:
Publisher's PDF, also known as Version of record

Queen Mary Law Research
Paper No. 364/2021

The Role of Patents and Licensing in the Governance of Human Genome Editing: A White Paper

Response to the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing Reports

Human Genome Editing: A Framework for Governance and Recommendations

30 July 2021

Duncan Matthews, Abbe Brown, Emanuela Gambini, Aisling McMahon, Timo Minssen, Ana Nordberg, Jacob S. Sherkow, Jakob Wested, Esther van Zimmeren*

* Professor Duncan Matthews, Queen Mary Intellectual Property Research Institute (QMIPRI), Centre for Commercial Law Studies, Queen Mary University of London, UK; Professor Abbe Brown, School of Law, University of Aberdeen, UK; Dr Emanuela Gambini, School of Law, Queen Mary University of London, UK; Dr Aisling McMahon, Department of Law, Maynooth University, Republic of Ireland; Professor Timo Minssen, Centre for Advanced Studies in Biomedical Innovation Law (CeBIL), Faculty of Law, University of Copenhagen, Denmark; Dr Ana Nordberg, Faculty of Law, Lund University, Sweden; Professor Jacob S Sherkow, College of Law, University of Illinois at Urbana-Champaign, USA; Dr Jakob Wested, Centre for Advanced Studies in Biomedical Innovation Law (CeBIL), Faculty of Law, University of Copenhagen, Denmark, and Data Analytics Center (DAC) of the Danish Medicines Agency; Professor Esther van Zimmeren, Faculty of Law, University of Antwerp, Belgium.

Abstract

On 12 July 2021 the World Health Organization (WHO) Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing published a set of reports entitled *Human Genome Editing: A Framework for Governance and Recommendations*. These reports provide valuable advice and recommendations on appropriate institutional, national and global governance mechanisms for human genome editing. The Expert Advisory Committee's *A Framework for Governance* highlights explicitly the role that patents and licences can play as a form of governance of human genome editing. The *Recommendations* state that the Committee 'believes that governance measures based on patents or [other forms of] intellectual property, when used together with other tools, may help strengthen the governance and oversight of human genome editing' [and that] 'It will be important to avoid using patents in ways that potentially prevent others from delivering similar capabilities at a cheaper cost'. This paper responds to the recommendations of the Expert Advisory Committee and elaborates further on the role that patents and licensing can play in the governance of human genome editing. It concludes with our own recommendations on how the role of patents and licensing can be considered further in the light of the WHO Expert Advisory Committee's reports.

1. Context and Purpose of the Paper

1.1. A Response to the WHO Expert Advisory Committee's Reports

On 12 July 2021 the World Health Organization (WHO) Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing published a set of reports entitled *Human Genome Editing: A Framework for Governance and Recommendations*.[1] The governance framework on human genome editing, together with the recommendations of the Expert Advisory Committee and a *Position Paper* which summarises these two publications, provide valuable advice and recommendations on appropriate institutional, national and global governance mechanisms for human genome editing.[2]

The Expert Advisory Committee's *A Framework for Governance* highlights explicitly the role that patents and licences may play as an avenue for a form of governance of human genome editing. This includes directing research investment towards certain areas as well as allowing patent holders to limit or even prohibit a particular use of a process or product.[3] *A Framework for Governance* elaborates the reasons why this governance role for patents and licences may be significant, acknowledging that 'patent holders may find themselves with a reasonable amount of influence over how a technology develops, by

[1] In 2019 the Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing (the Committee) was tasked by the Director-General of the WHO "to examine the scientific, ethical, social and legal challenges associated with human genome editing (both somatic and germ cell), with a direction to advise and make recommendations on appropriate institutional, national, regional and global governance mechanisms for both somatic and germline human genome editing"; WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: A Framework for Governance* (2021) <www.who.int/publications/i/item/9789240030060> accessed 23 July 2021, iii.

[2] Although the concept of governance is contested and multi-faceted, it is understood by the WHO Expert Advisory Committee's reports to be the norms, values and rules of the processes through which public affairs are managed so as to ensure transparency, participation, inclusivity and responsiveness. The Expert Advisory Committee has viewed good governance as an iterative, ongoing process that includes mechanisms for regular revision. The Committee has stated that, ideally, governance is proactive, not only reactive, promoting public confidence; it requires access to adequate resources, capacity and technical knowledge to educate, engage and empower members of the scientific, medical and health care communities as well as the public. As such, the Expert Advisory Committee has considered good governance to be value-based and principle-driven.WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: A Framework for Governance* (2021) <www.who.int/publications/i/item/9789240030060> accessed 23 July 2021, x.

[3] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: A Framework for Governance* (2021) <www.who.int/publications/i/item/9789240030060> accessed 23 July 2021, 34.

choosing whether to write in restrictions on particular uses when negotiating a licence'.[4] This, in the words of the Expert Advisory Committee, is 'an efficient method compared with legislative efforts to outline restrictions, which are often slow and usually need to proceed separately in every country. On the other hand, it is certainly not democratic, as the choice of whether to include restrictions is not made by the body politic'.[5]

In formulating its recommendations on the role of patents and licences, both the Expert Advisory Committee's *A Framework for Governance*[6] and its *Recommendations*[7] acknowledge the inputs of our research group as the result of our presentations and participation in discussions during a presentation for Expert Advisory Committee members on 3 November 2020. The Expert Advisory Committee's resulting *Recommendations* are instructive regarding patents and licences, stating that 'The Committee believes that governance measures based on patents or [other forms of] intellectual property, when used together with other tools, may help strengthen the governance and oversight of human genome editing. It will be important to avoid using patents in ways that potentially prevent others from delivering similar capabilities at a cheaper cost'.[8] The *Recommendations* go on to identify the relevant values and principles as being openness, transparency, honesty and accountability, responsible stewardship of science, caution, fairness, social justice, solidarity and global health justice.[9]

The actions proposed by the Expert Advisory Committee's *Recommendations* are to secure these relevant values and principles by [bringing] together relevant patents holders (and those with patents pending and those establishing or running relevant patent pools (often associated with complex technologies that require complementary patents to provide efficient technical solutions) to explore the possible use of intellectual property as

[4] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: A Framework for Governance* (2021) <www.who.int/publications/i/item/9789240030060> accessed 23 July 2021, 36.
[5] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: A Framework for Governance* (2021) <www.who.int/publications/i/item/9789240030060> accessed 23 July 2021, 36.
[6] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: A Framework for Governance* (2021) <www.who.int/publications/i/item/9789240030060> accessed 23 July 2021, 83-84.
[7] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: Recommendations* (2021) <www.who.int/publications/i/item/9789240030381> accessed 23 July 2021, 14.
[8] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: Recommendations* (2021) <www.who.int/publications/i/item/9789240030381> accessed 23 July 2021, 15.
[9] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: Recommendations* (2021) <www.who.int/publications/i/item/9789240030381> accessed 23 July 2021, 13.

a governance measure for human genome editing'.[10] The *Recommendations* recognise the practical considerations in terms of relevant patent holders perhaps being unwilling to limit the use of their inventions, and the likely unequal geographic distribution of patent holders given the location of current patent applications relevant to human genome editing.[11]

To implement these actions, the specific *Recommendations* of the Expert Advisory Committee are the following:

1. In collaboration with other international organizations, such as the World Intellectual Property Organization and the World Trade Organization and its Agreement on Trade-Related Aspects of Intellectual Property (the TRIPS Agreement),[12] WHO should encourage relevant patent holders to help ensure equitable access to human genome editing interventions. This may include licensing costs proportional to the economic situation of a country.

2. WHO should encourage industry to work with resource-constrained countries to build capacity to take advantage of human genome inventions.

3. WHO should convene a meeting of those holding or applying for patents relevant to human genome editing, industry bodies, international organizations such as the World Intellectual Property Organization and the World Trade Organization, and those involved in establishing or running relevant patent pools to explore the potential for the adoption of appropriate ethical licensing requirements.[13]

It is instructive to note that these *Recommendations* on intellectual property comprise one of the eight core themes that will be subject to review in no more than 3 years by the WHO's Science Division, taking into account scientific, technological, and societal

[10] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: Recommendations* (2021) <www.who.int/publications/i/item/9789240030381> accessed 23 July 2021, 15.
[11] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: Recommendations* (2021) <www.who.int/publications/i/item/9789240030381> accessed 23 July 2021, 15.
[12] World Trade Organization, Agreement on Trade-Related Aspects of Intellectual Property Rights (as amended on 23 January 2017), Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, signed in Marrakesh, Morocco on 15 April 1994 <www.wto.org/english/docs_e/legal_e/31bis_trips_01_e.htm> accessed 27 July 2021.
[13] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: Recommendations* (2021) <www.who.int/publications/i/item/9789240030381> accessed 23 July 2021, 15.

changes, adequacy of implementation and assessment of impact, and potential future needs or concerns.[14]

This White Paper focuses on these recommendations of the Expert Advisory Committee and elaborates the potential role that patents and licensing could play in the governance of human genome editing.[15] We conclude with suggestions as to how the role of patents and licensing can be considered further in the light of the WHO Expert Advisory Committee's reports.[16]

1.2. The Rationale for the Governance of Human Genome Editing

Since the publication in 2012 in 'Science' of the seminal paper by Nobel Laureates Jennifer Doudna and Emmanuelle Charpentier and their collaborators on the CRISPR-Cas9[17] technology for genome editing, the debate over the need for appropriate

[14] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: Recommendations* (2021) <www.who.int/publications/i/item/9789240030381> accessed 23 July 2021, xi.

[15] In the paper the term "genome editing" is drawn on in preference to "gene editing", as it refers to a broader set of practices which are not limited to the modifications of genes. This concept and term also includes the "modifications of the epigenome and regulatory sequences" and its scientific semantic field is considered wider than the term "gene editing". Nuffield Council on Bioethics, *Genome Editing and Human Reproduction: Social and Ethical Issues* (2018) <www.nuffieldbioethics.org/publications/genome-editing-and-human-reproduction> accessed 23 July 2021, iii, 2. Genome editing encompasses the practices "of making targeted interventions at the molecular level of DNA or RNA function, deliberately to alter the structural or functional characteristics of biological entities", which "include complex living organisms, such as humans and animals, tissues and cells in culture, and plants, bacteria and viruses". Nuffield Council on Bioethics, *Genome Editing: An Ethical Review* (2016) <www.nuffieldbioethics.org/publications/genome-editing-an-ethical-review> accessed 23 July 2021, iii, 4.

[16] The authors of this White Paper have benefitted from invaluable discussions with our Scientific Advisory Committee members: Professor Richard Ashcroft, Deputy Dean and Professor of Bioethics, City University, London; Nick Bassil, European Patent Attorney and Partner, Kilburn & Strode, London; Professor Peter Braude OBE FRCOG FRSB FMedSci, Emeritus Professor of Obstetrics and Gynaecology, King's College London; Professor Frances Flinter, Emeritus Professor of Clinical Genetics, Guy's and St Thomas' NHS Foundation Trust, London; Dr Andy Greenfield, Programme Leader, Medical Research Council (MRC) Harwell Institute, UK; Phil Hinchliffe, Biotech Examiner, European Patent Office; Dr Pete Mills, Assistant Director, Nuffield Council on Bioethics, London; Peter Thompson, Chief Executive, Human Fertilisation and Embryology Authority (HREA), UK. We are extremely grateful for their invaluable insights and guidance. Particular thanks also to Jamie Atkins, Counsel and European Patent Attorney, Kilburn & Strode, London, who participated in our presentations to the WHO Expert Advisory Committee in November 2020.

[17] CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) technology draws on the bacterial system of defence against viral attack in order to obtain systems for genome editing. In particular, the CRISPR-Cas9 technology was developed "from type II CRISPR-Cas systems, which provide bacteria with adaptive immunity to viruses and plasmids". Cas 9, which is the protein associated with CRISPR, "is an endonuclease that uses a guide sequence within an RNA duplex, tracrRNA:crRNA, to form base pairs with DNA target sequences enabling Cas9 to introduce a site-specific double-strand break in the DNA". The targeted double-strand genome breaks are, then, repaired the cellular repair pathways, NHEJ (non-homologous end joining) or HDR (homology-directed repair). CRISPR-Cas9 allows to "efficiently target, edit, modify, regulate, and mark genomic loci of a wide array of cells and organisms". Jennifer A Doudna and Emmanuelle Charpentier, 'The New Frontier of Genome Engineering with CRISPR- Cas9'(2014) 346(6213) Science 1077; Nuffield Council on Bioethics, *Genome Editing: An Ethical Review* (2016)

governance mechanisms for genomic engineering and human germline modification has intensified.[18] CRISPR-Cas9 technology was developed after other genome editing technologies, such as ZFNs and TALENs,[19] and provides a potentially cost-effective, precise and simple tool to edit the genome,[20] with a broad range of possible applications in biology, biomedicine and biotechnology: spanning from human gene therapy and the modification of the germ line to the development of new crops in agriculture and the engineering of animal research models.[21]

In April 2015 a group of prominent scientists and scholars recommended "to discourage, even in those countries with lax jurisdictions where it might be permitted, any attempts at germline genome modification for clinical application in humans, while societal, environmental, and ethical implications of such activity are discussed among scientific and governmental organizations".[22] As they pointed out, genome engineering technology provides "unparalleled potential for modifying human and non-human genomes", but nevertheless involves unknown risks for human health.[23]

In particular, the discussion about how to devise and establish the global governance of human genome editing heightened after a Chinese researcher at the Southern University of Science and Technology of China in Shenzhen, Dr. He Jiankui, announced on 25 November 2018, at the Second International Summit on Human Genome Editing in Hong Kong, that he used CRISPR-Cas9 technology to create the first genome-edited twin baby

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<www.nuffieldbioethics.org/publications/genome-editing-an-ethical-review> accessed 23 July 2021, iii, 8-9.

[18] Martin Jinek and others, 'A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity' (17 August 2012) 337(6069) Science 816. See also Jennifer A Doudna and Emmanuelle Charpentier, 'The New Frontier of Genome Engineering with CRISPR- Cas9' (2014) 346(6213) Science 1077.

[19] Zinc finger nucleases (ZFNs) were set forth in 2005 and transcription activator-like effector nucleases (TALENs) in 2010. Both ZFNs and TALENs are "proteins that work in a conceptually similar manner, containing one module that can be engineered to recognise a specific DNA sequence and guide a second, attached module to cut the DNA. ZFNs and TALENs are derived, respectively, from mammalian transcription factors (proteins in mammalian cells that bind to DNA and cause a gene to become active) and the plant pathogen, *Xanthomonas* sp. Although their protein frameworks differ, ZFNs and TALENs each contain a set of 'fingers' or 'repeats' that can be designed to recognise a selected DNA sequence with a high degree of specificity. (...) In both cases specificity is provided by combining multiple fingers/repeats and attaching this module to an enzyme that cuts one strand of DNA; ZFNs and TALENs each work in pairs to produce a double-strand break (a break at opposite points in the two entwined strands of the DNA molecule). (…) The role of ZFNs and TALENs is therefore to produce a targeted double-strand break in the genome, which the cellular machinery then repairs". Nuffield Council on Bioethics, *Genome Editing: An Ethical Review* (2016) <www.nuffieldbioethics.org/publications/genome-editing-an-ethical-review> accessed 23 July 2021, iii, 8.

[20] Jennifer A Doudna and Emmanuelle Charpentier, 'The New Frontier of Genome Engineering with CRISPR- Cas9' (2014) 346(6213) Science 1077.

[21] Jennifer A Doudna and Emmanuelle Charpentier, 'The New Frontier of Genome Engineering with CRISPR- Cas9' (2014) 346(6213) Science 1077.

[22] David Baltimore and others, 'A Prudent Path Forward for Genomic Engineering and Germline Gene Modification' (2015) 348(6230) Science 36, 37.

[23] Ibid.

girls,[24] disabling "a gene called CCR5, which forms a protein that allows HIV to enter a cell".[25] This announcement immediately led to criticism in the international scientific community (as well as being censured by bioethicists and legal scholars),[26] since Dr. Jiankui's work did not comply with the principles and practices of ethical clinical research.[27]

In the aftermath of this revelation, the National Academy of Sciences, Engineering, and Medicine (NASEM), the Chinese Academies of Science, and the Royal Society of the United Kingdom ("the Academies") convened a commission with the task of developing "a framework for scientists, clinicians, and regulatory authorities to consider when assessing potential clinical applications of human germline genome editing, should society conclude that heritable human genome editing applications are acceptable".[28]

The International Commission published the final Report "Heritable Human Genome Editing"[29] and at its presentation event, on 3 September 2020, acknowledged the discussions that they had with the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, which was set up in December 2018 to examine the scientific, legal ethical and social challenges associated with human genome editing (both somatic and germ cell genome editing),[30] on the global governance and oversight of human genome editing.

The issues raised by genome editing technologies are vast, as these technologies question the meaning of human dignity and integrity in different socio-cultural and political-economic contexts and require a critical consideration as to the uses of these technologies that are acceptable in pluralistic societies. However, some of these problems are not unfamiliar: the 1970s debate of the scientific community on the

[24] Henry T Greely, 'CRISPR'd Babies: Human Germline Genome Editing in the 'He Jiankui Affair"' (2019) 6(1) *Journal of Law and the Biosciences* 111.
[25] David Cyranoski and Heidi Ledford, 'Genome-Edited Baby Claim Provokes International Outcry (2018) 563 Nature 607.
[26] On the immediate reactions to Dr. Jiankui's announcement, see Robin Lovell-Badge, 'CRISPR Babies: A View from the Centre of the Storm' (2019) 146 Development 1, 2.
[27] Alta R Charo, 'Rogues and Regulation of Germline Editing' (2019) The New England Journal of Medicine; Sheldon Krimsky, 'Ten Ways in Which He Jiankui Violated Ethics' (2019) 17 Nature Biotechnology 19; Erika Kleiderman and Ubaka Ogbogu, 'Realigning Gene Editing with Clinical Research Ethics: What the 'CRISPR Twins' Debacle Means for Chinese and International Research Ethics Governance' (2019) 26(4) Accountability in Research 257, 260; Henry T Greely, 'CRISPR'd Babies: Human Germline Genome Editing in the 'He Jiankui Affair"' (2019) 6(1) *Journal of Law and the Biosciences* 111.
[28] The National Academies of Sciences, Engineering, Medicine, International Commission on the Clinical Use of Human Germline Genome Editing <www.nationalacademies.org/our-work/international-commission-on-the-clinical-use-of-human-germline-genome-editing#sectionWebFriendly> accessed 23 July 2021.
[29] The National Academies of Sciences, Engineering, Medicine, *Heritable Human Genome Editing* (2020) <www.nap.edu/download/25665> accessed 23 July 2021.
[30] WHO, 'Call for Contribution: Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing - Now Closed' <www.who.int/news-room/articles-detail/call-for-contribution-advisory-committee-on-developing-global-standards-for-governance-and-oversight-of-human-genome-editing> accessed 23 July 2021.

governance of recombinant DNA[31] and its biohazards already involved a technology that allowed scientists to make and "outdo evolution", as the microbiologist and Nobel Laureate David Baltimore remarked referring to rDNA.[32]

The model of governance for rDNA technology emerged from the second Asilomar Conference, held on 24-27 February 1975, which was focused on examining the potential risks and benefits of rDNA and addressed their containment.[33] and promoted the establishment, in 1976, of the Guidelines for Research Involving Recombinant DNA Molecules,[34] the regulatory framework for researchers that inspired several states, such as Germany, France and the United Kingdom.[35]

This Asilomar model based on the responsible self-regulation initiative of the scientific community is deemed to have provided a successful model of governance for rDNA technology, in terms of establishing an "effective safety regime" and "gaining the public's trust".[36] At present, this model is still regarded by its leading organizers as exemplary to address and solve the problems related to human genome editing.[37]

According to the scientist Paul Berg, one of the leading organisers of the Asilomar Conference, the model that emerged from Asilomar allowed "geneticists to push research to its limits without endangering public health".[38] It has been questioned, however, whether it shall be regarded as the reference model to draw upon in order to deal with the specific scientific, ethical, legal and policy challenges that the democratic governance of human genome editing involves, because of its extensive potential to alter the human genome, and in general the governance of science and emerging technologies.[39] In

[31] Recombinant DNA technology enabled the cutting and splicing together of DNA molecules and was applied to bacteria and then, to multicellular organisms. See Paul Berg and J E Mertz, 'Personal Reflections on the Origins and Emergence of Recombinant DNA Technology' (2010) 184(1) Genetics 9-17.

[32] Liebe F Cavalieri, *The Double-Edged Helix: Genetic Engineering in the Real World* (Columbia University Press 1981) 1, 32. Michael Rogers, *Biohazard* (Alfred A Knopf 1977), 52.

[33] Sheldon Krimsky, 'From Asilomar to Industrial Biotechnology: Risks, Reductionism and Regulation' (2005) 14(4) Science as Culture 309.

[34] National Institutes of Health, 'Guidelines for Research Involving Recombinant DNA Molecules', *Federal Register*, No. 41, 7 July 1976, 27902-27943. These guidelines replaced the recommendations contained in the 1975 Summary Statement of the Asilomar Conference.

[35] Sheldon Krimsky, *Genetic Alchemy. The Social History of the Recombinant DNA Controversy* (The MIT Press 1985), 126-127. Herbert Gottweis, *Governing Molecules. The Discursive Politics of Genetic Engineering in Europe and the United States*, (The MIT Press 1998), 104-105.

[36] Paul Berg, 'Asilomar 1975: DNA Modification Secured' (18 September 2008) 455 Nature 290, 291. Paul Berg, 'Reflections on Asilomar 2 at Asilomar 3' (2001) 44(2) Perspectives in Biology and Medicine 183.

[37] David Baltimore and others, 'A Prudent Path Forward for Genomic Engineering and Germline Gene Modification' (2015) 348(6230) Science 36.

[38] Paul Berg, 'Asilomar 1975: DNA Modification Secured' (18 September 2008) 455 Nature 290.

[39] Sheila Jasanoff, J Benjamin Hurlbut, Krishanu Saha, 'CRISPR Democracy Gene Editing and the Need for Inclusive Deliberation' (2015) Issues in Science and Technology 25, 26; Sheila Jasanoff, J Benjamin Hurlbut, Krishanu Saha, 'Democratic Governance of Human Germline Genome Editing' (2019) 2(5) The CRISPR Journal 266. See also Shobita Parthasarathy, 'Governance Lessons for CRISPR/Cas9 from the Missed Opportunities of Asilomar' (2015) 6(3-4) Ethics in Biology, Engineering & Medicine – An International Journal 305; Krishanu Saha and others, 'Building Capacity for a Global Genome Editing Observatory: Institutional Design (2016) 36(8) Trends in Biotechnology 741; J Benjamin Hurlbut,

particular, part of the scholarship pointed out that Asilomar set out an inadequate model of deliberation and representation, because of the exclusions of relevant lay and expert perspectives and its agenda was limited: ethical and biosecurity issues were mostly left out of the discussion, together with the problems regarding biodiversity and food security, and the questions about intellectual property (IP) were totally ignored.[40]

The governance model that emerged from the Asilomar Conference in 1975 and the debate over the biohazards and ethical and social implications of genetic engineering took place in a largely different national and international regulatory IP environment. It was developed before the approval in 1980 in the United States of the Bayh-Dole Act[41] and the Stevenson-Wydler Technology Innovation Act[42] that fostered non-profit organisations, such as universities, to patent the inventions resulting from government-sponsored research and the transfer of technology from federal laboratories.[43]

By 1980, the patent eligibility of the products of genetic engineering, which involved microorganisms and organisms, had still to be established in the United States by the Supreme Court's judgement in *Diamond v. Chakrabarty*.[44] Moreover, the Asilomar Conference happened before the adoption of the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (the TRIPS Agreement) signed in 1994[45] that set out global standards for IP protection that are crucial, at present, for devising the IP governance of human genome editing.

The major patent on rDNA technology, the so-called Cohen-Boyer rDNA cloning patent, was granted in 1980[46] and was non-exclusively licensed (see Section 2.4.2 *Non-exclusive Licensing* and Sections 2.4 *Private Governance* and 2.4.1 *Exclusive Licensing* that examine and discuss specifically patent licensing issues), allowing this enabling and foundational technology to be widely available to researchers and the developing biotech

'Imperatives of Governance: Human Genome Editing and the Problem of Progress' (2020) 62(1) Perspectives in Biology and Medicine 177.

[40] Sheila Jasanoff, J Benjamin Hurlbut and Krishanu Saha, 'CRISPR Democracy Gene Editing and the Need for Inclusive Deliberation' (2015) Issues in Science and Technology 25, 27-28.

[41] Act of Dec. 12, 1980, Pub. L. No. 96-517, 94 Stat. 3015-28 (codified as amended at 35 U.S.C. §§ 200-211, 301-307 (1994).

[42] Stevenson-Wydler Technology Innovation Act of 1980, Pub. L. No. 96-480, 94 Stat. 2311-2320 (codified as amended at 15 U.S.C. §§3701- 3714 (1994).

[43] Rebecca S Eisenberg, 'Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research' (1996) 82(8) Virginia Law Review 1663, 1665. See also David C Mowery and others, 'The Growth of Patenting and Licensing by U.S. Universities: An Assessment of the Effects of the Bayh-Dole Act of 1980' (2001) 30 Research Policy 99; Rosa Grimaldi and others, '30 Years after Bayh-Dole: Reassessing Academic Entrepreneurship' (2011) 40 Research Policy 1045.

[44] *Diamond v. Chakrabarty* 447 U.S. 303 (1980); 206 USPQ 193 (The Supreme Court of the United States).

[45] World Trade Organization, Agreement on Trade-Related Aspects of Intellectual Property Rights (as amended on 23 January 2017), Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, signed in Marrakesh, Morocco on 15 April 1994 <www.wto.org/english/docs_e/legal_e/31bis_trips_01_e.htm> accessed 27 July 2021.

[46] Stanley N Cohen and Herbert W Boyer, "Process for Producing Biologically Functional Molecular Chimeras", United States Patent 4,237,224, 2 December 1980.

industry.[47] The Office of Technology Licensing (OTL) of Stanford University, which dealt with the patenting and licensing of the rDNA cloning patent, however at that time felt the need to solicit the views of the NIH about getting patent protection on rDNA discoveries publicly funded[48] because of the patent "political sensitivity".[49] Although the NIH supported Stanford University's patenting plan, they established that "each agreement would be amended in order to allow the university to grant a license only if the licensee provided assurances of compliance with the standards of physical and biological containment"[50] set out in the Guidelines for Research Involving Recombinant DNA Molecules, which were compulsory only for academic researchers until 1981.[51]

In addressing the complex problems involved in human genome editing, several scholars have pointed out the significant role that patent systems play in devising and articulating its governance[52] and have analysed how different forms of private governance have already been employed and established.

In this respect, this White Paper fills a gap in the wider policy debate, alongside the WHO Expert Advisory reports, regarding the implications for the global governance of human genome editing and discusses how the use of these technologies have already been shaped and regulated by private actors alongside regional or national patent law and examination practices, taking into account the flexibilities available under international patent treaties.[53] In this paper, we combine an analysis of the potential of *private governance* through patenting and licensing strategies and *public governance* in shaping national patent law in contributing to regulating human genome editing.

This White Paper, nevertheless, highlights that the global governance of human genome editing cannot rest only on patent systems and law but requires a more inclusive

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[47] Sally Smith Hughes, 'Making Dollars Out of DNA: The First Major Patent in Biotechnology and the Commercialization of Molecular Biology, 1974-1980' (2001) 92(3) Isis 541, 569.

[48] Donald S Fredrickson, the former director of the NIH, in June 1976 received a letter from Stanford University to solicit the NIH views about getting patent protection on rDNA discoveries that was perceived as a "modestly seismic event, a nervous shift at the conjunction of the academic/not-for-profit and commercial tectonic plates sustaining the crust of the biomedical research enterprise". Donald S Fredrickson, *The Recombinant DNA Controversy: A Memoir. Science, Politics and the Public Interest 1974-1981* (American Society for Microbiology Press 2001) vii, 93.

[49] Sally Smith Hughes, 'Making Dollars Out of DNA: The First Major Patent in Biotechnology and the Commercialization of Molecular Biology, 1974-1980' (2001) 92(3) Isis 541, 565.

[50] Donald S Fredrickson, *The Recombinant DNA Controversy: A Memoir. Science, Politics and the Public Interest 1974-1981* (American Society for Microbiology Press 2001) vii, 99-100.

[51] Sheldon Krimsky, *Genetic Alchemy. The Social History of the Recombinant DNA Controversy* (The MIT Press 1982), viii, 193.

[52] Shobita Parthasarathy, 'Use the Patent System to Regulate Gene Editing' (25 October 2018) 562 Nature 486; Anu Shukla-Jones, Steffi Friedrichs and David E Winickoff (2018), "Gene Editing in an International Context: Scientific, Economic and Social Issues across Sectors", OECD Science, Technology and Industry Working Papers (2018)
</www.oecd-ilibrary.org/docserver/38a54acb-en.pdf?expires=1627315711&id=id&accname=guest&checksum=E6EEDDD33550D7D9758A0D703FDA55CD> accessed 23 July 2021.

[53] Nienke de Graeff and others, 'Fair Governance of Biotechnology: Patents, Private Governance, and Procedural Justice' 2018) 18(12) The American Journal of Bioethics 57.

democratic deliberative process in order to define which uses of these technologies are socially acceptable and how they should be regulated. Furthermore, it emphasises that although IP governance measures for human genome editing can contribute to its oversight, they shall be "integrated into a broader governance framework".[54]

Governance is not an unequivocal term. The concept is used in different manners by various disciplines. The WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing endorsed in its report *Human Genome Editing; A Framework for Governance*, the UNESCO description of governance.[55] Governance has been understood 'to include the norms, values and rules of the processes through which public affairs are managed so as to ensure transparency, participation, inclusivity and responsiveness' and linked to 'structures and processes that are designed to ensure accountability, transparency, responsiveness, rule of law, stability, equity and inclusiveness, empowerment, and broad-based participation'.[56]

This description, however, tends to focus on the public governance perspective. The Committee broadens this perspective in its section on good governance. The Committee has recognised that principles of good governance include formal regulation pursuant to legislation or judicial opinion, and also encompass a system of norms as well as influence, and including forces to shape the direction and conditions of research and applications, such as well-crafted public and private funding priorities and conditions. It recognises that countries, organizations and institutions with formal approvals or prohibitions should include mechanisms for revisiting earlier policies (laws, regulations, guidelines, etc.) in light of technical, practical and ethical developments. Good governance also includes a commitment to share accurate, evidence-informed, accessible and timely information about the relevant science. It includes professional and industrial best practices, peer review and ethics assurance by publishers, amongst other measures.

In this paper we align with the broad perspective of governance adopted by the Committee. Obviously, the line between private and public governance will not always be clear, as patents are private property rights granted by public authorities (patent offices) and are held by both private and public entities. Patent law and policy is developed in a largely multilevel governance context (international, regional, national) where a variety of legislative, executive and judicial actors is operating. Private and public organizations

[54] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: Recommendations* (2021) <www.who.int/publications/i/item/9789240030381> accessed 21 July 2021, 15.
[55] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: A Framework for Governance* (2021) <www.who.int/publications/i/item/9789240030060> accessed 23 July 2021, 10.
[56] United Nations Educational, Scientific and Cultural Organization (UNESCO) <www.ibe.unesco.org/en/geqaf/technical-notes/concept-governance> accessed 23 July 2021.

apply for patent protection and exploit their private property rights once granted and can steer the use of patented technologies through their private contracting practices (patent licensing). We identify public and private actors as core actors in the patent context, which could play a crucial role in the governance of human genome editing.

2. Patents as a Governance Tool

2.1. Patent Basics

Patents are negative exclusionary rights that give their holders the right to prevent others from practising the invention claimed in the patent. Patent rights are limited in time, typically 20 years from the date the underlying patent application was filed.[57] Patents are examined by national or regional patent offices to ensure the invention, as claimed, meets several substantive standards of invention—namely, that the invention is novel, that it contains an "inventive step" over the state of the art at the time and that it possesses sufficient utility. Many patent offices require that the patent application itself sufficiently disclose the invention to allow others to practice it. Other patent offices (the US in particular) may impose additional requirements regarding disclosure. In addition, and as discussed in detail below, some jurisdictions contain specific prohibitions concerning the patenting of certain technologies.[58]

These substantive minimum requirements for patentability are largely harmonized through a series of international treaties. The TRIPS Agreement, in particular, establishes the rights and obligations regarding patentability for all WTO Member countries. The TRIPS Agreement requires its signatories to provide for minimum standards of patentability, protection, and enforcement. The WTO Dispute Settlement Body has also issued several important decisions interpreting the TRIPS Agreement.[59]

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[57] Article 33, TRIPS Agreement, provides: "The term of protection available shall not end before the expiration of a period of twenty years counted from the filing date". World Trade Organization, Agreement on Trade-Related Aspects of Intellectual Property Rights (as amended on 23 January 2017), Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, signed in Marrakesh, Morocco on 15 April 1994 <www.wto.org/english/docs_e/legal_e/31bis_trips_01_e.htm> accessed 27 July 2021.

[58] See for instance Article 6(2)(b) Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions [1998] OJ L213/13; see Ana Nordberg and others, 'Cutting Edges and Weaving Threads in the Gene Editing (Я)evolution: Reconciling Scientific Progress with Legal, Ethical, and Social Concerns' (2018) 5(1) Journal of Law and the Biosciences 35; Duncan Matthews, 'Access to CRISPR Genome Editing Technologies: Patents, Human Rights and the Public Interest' (2020), Queen Mary School of Law Legal Studies Research Paper No. 332/2020, <https://ssrn.com/abstract=3595392> accessed 27 July 2021.

[59] For a useful overview of the TRIPS Agreement see World Trade Organization, 'Overview: the TRIPS Agreement' <https://www.wto.org/english/tratop_e/trips_e/intel2_e.htm> accessed 23 July 2021, and for the full text version of the TRIPS Agreement, see World Trade Organization, Agreement on Trade-Related Aspects of Intellectual Property Rights (as amended on 23 January 2017), Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, signed in Marrakesh, Morocco on 15 April 1994 <www.wto.org/english/docs_e/legal_e/31bis_trips_01_e.htm> accessed 27 July 2021.

At the same time, there is no uniform international patent system. An applicant for a patent wishing to protect the claimed invention in a given jurisdiction must file the application there either directly or using a patent cooperation international or regional mechanism allowing for simultaneously filing for a patent in several or multiple countries. Furthermore, patent enforcement is territorial: a patent granted in a particular country is only enforceable within the borders of that country's jurisdiction.

In some instances, patents can be revoked or cancelled after they have been granted. The US Patent and Trademark Office (USPTO), for example, has several administrative procedures for challenging patents once they have been issued, including *inter partes* and post-grant reviews and re-examination. The European Patent Office (EPO), similarly, has opposition proceedings to contest already issued patents. Such post-issuance administrative procedures are often limited by time (e.g., for the 9-month period following the issuance of the patent, in the case of European opposition proceedings) and grounds of challenge. Similarly, the Brazilian Patent Office (INPI) offers an administrative procedure allowing opponents with a legitimate interest to request the invalidation of a patent granted during the preceding 6 months.[60] The Indian Patent Office offers pre-grant opposition proceedings on equivalent grounds, so that third parties can challenge patents even before they are issued.[61] If patent owners believe their patents are infringed, they can bring the alleged infringer before the court. In an increasing number of countries, these courts will be specialized courts with expertise in intellectual property law, or even specifically in patent law. Courts, specialized and non-specialized, hence also play a core role in shaping patent law, policy and *(public) governance* in interpreting patentability requirements, exclusions to patentability and exceptions.

It is important to reiterate that patents are *exclusionary entitlements* and not *positive rights*; they do not affirmatively allow the patent holder to practice the underlying invention. Where the claimed technology is otherwise regulated by law, the patent holder may be prevented from using or placing in the market the claimed technology, such as the case with patents covering new medical therapeutics not yet approved by the appropriate regulatory authority.

In a general sense, and as detailed below, patents' right to exclude give their holders the power to license the claimed technology to others. This can be done exclusively, i.e., vested in a single third-party (excluding also the patent owner), or non-exclusively, that is, among a number of licensees. Patent holders can use patent licensing to, among other structures, establish spin-offs, startups, and collaborative research and development agreements. This is a common concern where multiple different entities hold patents covering components or aspects of a complex technology. Without agreement among the

[60] Article 50, Brazilian Industrial Property Law No. 9279 of 14 May 1996 as amended on 18 March 2013 (LEI Nº 9.279 de 14 de Maio de 1996) <www2.camara.leg.br/legin/fed/lei/1996/lei-9279-14-maio-1996-374644-norma-pl.html> accessed 27 July 2021 .

[61] The grounds for bringing pre-grant opposition against the grant of a patent are set out in Section 25 of the Indian Patents Act, India The Patents Act 1970 <https://ipindia.gov.in/writereaddata/Portal/IPOAct/1_31_1_patent-act-1970-11march2015.pdf> accessed 27 July 2021.

patent-holders in such an instance, each has the right to exclude the other from practicing the larger technology, for example to develop a product and place it in the market, which means that society cannot benefit from it. Aside from these concerns, patent licensing activity also gives rights holders control over how claimed technologies are practiced, by whom, and under what conditions. In these ways, patents can be an instrument of *private governance* insofar as they establish limits over how a patented technology is developed and used.[62]

2.2. Patents on genome editing technologies: A fragmented global picture with pending litigations and uncertainties

As will be elaborated below, right holders may exploit their patents in many different ways. Their strategy will depend on a range of factors, such as the ambitions and goals of rights holders, the nature and applications of the patented technology, the competitive environment, as well as the scope, significance and validity of relevant exclusivities.[63] So far, hundreds of patents, directed to genome editing technologies, have been granted by patent offices across the world, with many more applications still under examination.[64] Moreover, many pending patent litigations and disputes over different aspects of genome editing technologies are currently unresolved, which has resulted in considerable legal uncertainty. In addition, it is important to note that patents are also sought for other genome editing technologies, including meganucleases, zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and fundamental gene editing tools, such as genome editing vectors.[65] This complexity resulted in a rich diversity of patents and models of technology transfer, but it has also resulted in competitive struggles over the control of the technologies at both the pre-grant and post-grant level.[66]

Against this background it is clear that any discussion regarding the role of patents in genome editing governance must carefully consider the rapidly evolving patent landscape, including information of the prevalent forms of patents claims, licensing models, patentees and regional differences around the globe. It is therefore important to continuously monitor the outcome of patent litigations and regulatory developments, as

[62] Aiisling McMahon, 'Biotechnology & Patents as Private Governance: The Good, the Bad, the Potential for Ugly?' (2020) 3 Intellectual Property Quarterly 161; Esther van Zimmeren, 'Towards a New Patent Paradigm in the Biomedical Sector? Facilitating Access, Open Innovation and Social Responsibility in Patent Law in the US, Europe and Japan' (PhD thesis, KU Leuven2011).

[63] Note that exclusivities may be protected and enforced through other forms of IP which may affect patent strategies.

[64] See Diana Kwon, 'A Brief Guide to the Current CRISPR Landscape', <www.the-scientist.com/news-opinion/a-brief-guide-to-the-current-crispr-landscape--66128> accessed 27 July 2021.

[65] For more details and a good overview of these technologies, see Gregory D Graff and Jacob S Sherkow, 'Models of Technology Transfer for Genome-Editing Technologies' (2020) 21(1) Annual Review of Genomics and Human Genetics 509.

[66] Gregory D Graff and Jacob S Sherkow (2020), 'Models of Technology Transfer for Genome-Editing Technologies' (2020) 21(1) Annual Review of Genomics and Human Genetics 509.

was the case for example with the ruling by the Court of Justice of the European Union (EU) holding that precise genome editing technologies would not be exempted from European GMO law.[67]

2.2.1. The current patent landscape for CRISPR gene editing technologies

Several landscaping studies have been conducted in the area, mostly focusing on patents and revealing substantial global differences across the genome editing technology landscape.[68] A common finding appears to be that the number of patents and patent applications, the procedures for patent prosecution, as well as the question of patent ownership and the licensing of gene editing technologies, such as CRISPR, varies considerably in various patent systems. Accordingly, what can be claimed as patentable and on which terms – if at all – human genome editing technologies are licensed can differ across regions.[69] Whereas the area continues to evolve rapidly, the following provides a very short overview of one of the most recent and comprehensive data records focusing on CRISPR technology.

Recent 2020 CRISPR patent landscaping data from the independent patent analytics provider IPStudies, based in Switzerland, demonstrates that the current global patent landscape is highly fragmented with thousands of CRISPR patent families that cover the same or similar content filed in different patent jurisdictions.[70] The report shows a steep rise from only 96 CRISPR-related patent families to be found in the genome editing patent

[67] C-528/16 *Confédération paysanne and Others* v Premier ministre, Ministre de l'Agriculture, de l'Agroalimentaire et de la Forêt [2018] <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:62016CJ0528&from=en> accessed 27 July 2021.

[68] See e.g. '2020 CRISPR Patent Landscape – Where Do We Stand?' (*IPStudies*) <www.ipstudies.ch/2020/10/2020-crispr-patent-landscape-where-do-we-stand/> accessed 27 July 2021; Paramita Ghosh, 'Patent Landscape of CRISPR/Cas' in Anjanabha Bhattacharya, Vilas Parkhi and Bharat Char (eds) *CRISPR/Cas Genome Editing. Concepts and Strategies in Plant Sciences* (Springer 2020) 213; Jacqueline Martin-Laffon, Marcel Kuntz and Agnes E Ricroch, 'Worldwide CRISPR Patent Landscape Shows Strong Geographical Biases' (2019) 37(6) Nature Biotechnology 613.; Jacob S Sherkow, 'The CRISPR Patent Landscape: Past, Present, and Future' (2018) 1(1) CRISPR Journal 5–9; see WIPO, 'Patent Landscape Reports by Other Organizations' <www.wipo.int/patentscope/en/programs/patent_landscapes/plrdb_search.jsp?territory_code=CH> accessed 27 July 2021.

[69] ibid.

[70] "2020 CRISPR Patent Landscape – Where Do We Stand?' (*IPStudies*) <www.ipstudies.ch/2020/10/2020-crispr-patent-landscape-where-do-we-stand/> accessed 27 July 2021.

landscape in Spring 2014, to more than 7400 patent families[71] in their 2020 records – "and adding an average of 200 more every month in 2020".[72]

Moreover, the IPStudies data records from 2016 to 2020 indicate that "the high-level CRISPR patent landscape trends have been remarkably stable over the past 4 years, with continued patenting competition primarily among academic players in China and the USA".[73] While other national players from Europe, Asia and the Americas are certainly also engaged in considerable patenting, it is clear that China very quickly and successfully "joined the CRISPR race with a strong focus on the CAS9 technology for genome editing applications in particular in agriculture."[74] It is therefore not surprising that the Chinese Academy of Agricultural Sciences (42 institutes) takes the 3rd worldwide rank in the IPStudies landscape.[75]

Concerning the situation in the US, the IPStudies patent data highlight a fierce competition not only in CRISPR-related science, but also in the race to the patent office between the main academic rivals, i.e. the Broad Institute (of Harvard and MIT), which is the home institution of Feng Zhang et al., and the University of California, which employs Jennifer Doudna.[76] Furthermore, the datasets confirm that "both license their core CRISPR technology IP to a number of large industrial players, such as DuPont in agricultural applications, as well as to a set of pioneering CRISPR spin-offs primarily heading for therapeutic applications, namely Editas Medicine out from the Broad Institute, CRISPR Therapeutics initially funded by Emmanuelle Charpentier, and Intellia Therapeutics out from the University of California."[77]

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[71] A patent family is initiated by an initial invention filing at a patent office. In general, an invention will be ultimately recorded as different patents from the same "patent family": one or more patents per country, depending on the patent owner's investments in this country and the examination of patent applications by the national patent office. For instance, the initial invention by Doudna, Charpentier and their respective teams as filed at the USPTO on 25 May 2012 by the University of California has resulted in dozens of patent publications worldwide, several of which were just published at the USPTO in the past few weeks.

[72] '2020 CRISPR Patent Landscape – Where Do We Stand?' (*IPStudies*) <www.ipstudies.ch/2020/10/2020-crispr-patent-landscape-where-do-we-stand/> accessed 27 July 2021.

[73] ibid.

[74] ibid.

[75] ibid, acknowledging that "Patent quantitative metrics are subject to some statistical bias in favor of Chinese players, due to their earlier patent publication practice compared to other countries. Indeed, many patent applications are published by the CNIPA 3 months after their filing in China, while they are kept secret for 18 months in most other patent offices worldwide and in particular at the USPTO, the EPO and the WIPO".

[76] ibid.

[77] ibid. For a discussion of the problems related to this complex licensing landscape see Vincent M de Grandpré and Felicia Lozon, 'Making Sense of the Battle for the CRISPR-Cas9 Patent Rights' (*Osler*, 15 March 2021) <www.osler.com/en/resources/critical-situations/2021/making-sense-of-the-battle-for-the-crispr-cas9-patent-rights> accessed 27 July 2021 (explaining the impact of US decisions on the Canadian litigation).

The IPStudies data also discloses that in the set of 7427 patent families, “3078 address therapeutic applications, 996 animal modification, 1232 plant modification, and 541 bioproduction”, whereas as “more than 1850 institutes and companies worldwide have filed at least one patent application on their CRISPR R&D.”[78] The number of patent families addressing therapeutic applications is indeed astonishing. Yet, it should not be forgotten that leading scientists do not only praise the enormous therapeutic possibilities for genome editing technologies. They also point out that the “adaptation of microbial machineries to meet human needs is not guaranteed to succeed”.[79] Regarding the CRISPR-based technology they highlight in particular the need for interdisciplinary collaboration and warn that “the simplicity of its design and utilization should not disguise the importance of openly sharing valuable resources [...], which has encouraged cross-validation and speedy adoption of the technology for novel applications and will continue to foster rapid scientific and technological advances.” [80]

Notwithstanding these challenges, the IPStudies data further shows an increasing diversification and number of follow-on inventions building upon earlier patented technology and becoming public domain in the next 2-3 decades. IPStudies note that “the development of more than 50 shades of CRISPR in the past 4-5 years, as design arounds and/or improvements to the initial Cas9 discovery”, to which “about 4500 patent families specifically relate in our latest records. In contrast, back in 2014, all the IP derived from the 2012 discovery was Cas9 specific; its most famous alternative protein, Cpf1, now already gathers 899 patent families in the current landscape.”[81]

The IP Studies report finally finds that some commercial utilizations are still facing a challenging environment due to “the legal uncertainty around the unclear CRISPR licensing requirements in some jurisdictions, in particular for the above-mentioned most popular CRISPR system variants.” However, notwithstanding this legal uncertainty, which will be explained further below, the IPStudies 2020 data recorded close to “200 publicly announced licensing agreements, some exclusive, some non-exclusive, on a diversity of CRISPR technologies and application fields. More than half of those agreements were directly or indirectly issued from the competing Broad Institute and the University of California CRISPR IP portfolios.”[82]

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[78] ibid.
[79] Dan Wang, Feng Zhang, and Guangping Gao, ‘CRISPR-Based Therapeutic Genome Editing: Strategies and In Vivo Delivery by AAV Vectors’ (2020) 181(1) Cell 136.
[80] ibid.
[81] ‘2020 CRISPR Patent Landscape – Where Do We Stand?’ (*IPStudies*) <www.ipstudies.ch/2020/10/2020-crispr-patent-landscape-where-do-we-stand/> accessed 27 July 2021.
[82] Ibid.

2.2.2. Ongoing litigation: The CRISPR Cas-9 battle in the US and Europe

CRISPR Cas-9 technologies have been subject to considerable and ongoing litigation involving challenges around who should hold patents over such technologies. A highly contested global patent landscape has emerged, which resulted in legal uncertainty. The main dispute in this context in the US and Europe, relates to patent claims over CRISPR Cas-9 technologies asserted by University of California (UC) Berkeley (where Prof Doudna's team worked, and in collaboration with Prof Charpentier, now at Max Planck), and Broad Institute MIT and Harvard (involving a research team led by Prof Feng Zhang). While the ongoing patent battles over claims directed to CRISPR-Cas9 technology within the European and US patent system have probably attracted most attention, disputes over these patents are also raging in other countries and regions such as Asia and South America.[83] Many of these disputes have evolved around the issues of priority[84] and the novelty requirements. These proceedings are often inter-related and they are monitored carefully around the globe, since decisions on priority claims in e.g. the U.S. or European patent systems, often have a significant effect on the outcomes in pending litigations in other countries.[85] For this reason and for the sake of brevity, the following description of recent developments in patent litigation will primarily concentrate on US and European disputes.

As for the U.S., Professors Doudna, Charpentier and their collaborators were named as co-inventors for U.S. Patent Application No. 13/842,859, filed by the University of California, the University of Vienna and Charpentier on 15 March 2013, with a priority date of 25 May 2012 when the original provisional application was filed at the U.S. Patent and Trademark Office (USPTO). The patent application was particularly broad in scope, listing 155 claims to the general CRISPR technology.[86]

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[83] See e.g. John A Tessensohn, 'Japanese CRISPR Patent and Biotech Developments in the Early Reiwa Era' (2021) 40(3) Biotechnology Law Report 1.

[84] For further explanation see Vic Lin, 'What Is a Patent Priority Claim?', (*Patent Trademark Blog/IP Q&A*) <www.patenttrademarkblog.com/patent-priority-claim/> accessed 27 July 2021: "A priority claim is a helpful, and often critical, way to link a later-filed patent application to an earlier-filed patent application. Known as a priority application, the earlier-filed application must generally have common subject matter and common inventorship in order for a priority claim to be made. The common subject matter in the later-filed application will be backdated to the earlier filing date (priority date) of the earlier-filed application. The earlier-filed application may be a US priority application or foreign priority application, or a PCT application".

[85] See Vincent M de Grandpré and Felicia Lozon, 'Making Sense of the Battle for the CRISPR-Cas9 Patent Rights' (*Osler*, 15 March 2021) <www.osler.com/en/resources/critical-situations/2021/making-sense-of-the-battle-for-the-crispr-cas9-patent-rights> accessed 27 July 2021 (explaining the impact of US decisions on the Canadian litigation).

[86] Robin Feldman, 'The CRISPR Revolution: What Editing Human DNA Reveals about the Patent System's DNA' (2016) 64 UCLA Law Review Discourse 392, 401; see Jef Akst, 'UC Berkeley Receives CRISPR Patent in Europe' (24 March 2017) The Scientist <www.the-scientist.com/?articles.view/articleNo/48987/title/UC-Berkeley-Receives-CRISPR- Patent-in-Europe/> accessed 27 July 2021. For a good summary of the history of the proceedings see Vincent M de Grandpré and Felicia Lozon, 'Making Sense of the Battle for the CRISPR-Cas9 Patent Rights' (*Osler*, 15 March 2021)

Professor Feng Zhang and Professor Geoge Church's Broad Institute patent application to the USPTO, U.S. Patent No. 8,697,359, was filed later with a priority date of 12 December 2012, seven months after the Doudna, Charpentier and collaborators' priority date. The Broad Institute patent was nevertheless deemed eligible for a special accelerated examination track and the patent was issued by the USPTO on 15 April 2014.[87] The USPTO granted the key patent over the foundational CRISPR technology to the Broad Institute following interference proceedings with the University of California (Federal Circuit appeal pending).[88]

The outcome of the USPTO Patent Trial and Appeal Board (PTAB), rendering judgment that there was no interference-in-fact between the claims in interference between the University of California and the Broad Institute.[89] Broad persuaded the PTAB that the parties claim patentably distinct subject matter, rebutting the presumption of interference. Broad convinced the PTAB that its claims, which were all limited to CRISPR-Cas9 systems in a eukaryotic environment, are not drawn to the same invention as the University of California's, the latter which were all directed to CRISPR-Cas9 systems not restricted to any environment.[90] Specifically, the evidence showed the PTAB that the invention of such systems in eukaryotic cells would not have been obvious over the invention of CRISPR-Cas9 systems in any environment, including in prokaryotic cells or in vitro, because the ordinary person skilled in the art would not have reasonably expected a CRISPR-Cas9 system to be successful in a eukaryotic environment.[91]

In 2017, the PTAB terminated interference proceedings upon accepting Broad's argument that its claims pertaining to eukaryotic cells are sufficiently distinct from the University of California's claims for use in any environment, meaning there was no "interference in fact," a threshold requirement rooted in 37 C.F.R. § 41.203(a) U.S.C. The University of

<www.osler.com/en/resources/critical-situations/2021/making-sense-of-the-battle-for-the-crispr-cas9-patent-rights> accessed 27 July 2021.

[87] See also Jacob S Sherkow, 'The CRISPR Patent Interference Showdown Is On: How Did We Get Here and What Comes Next?' (*Stanford Law School Blogs/ Law and Biosciences Blog*, 29 December 2015) <https:/law.stanford.edu/2015/12/29/the-crispr-patent-interference-showdown-is-on-how-did-we-get-here-and-what-comes-next/> accessed 27 July 2021.

[88] A patent interference is an administrative proceeding in accordance with 35 U.S.C. §135 (pre AIA version) by which the USPTO Board of Patent Appeals and Interferences determines who was the first to invent the claimed subject matter. It typically concerns situations when two or more pending patent applications, or at least one pending patent application and an unexpired patent, contain patent claims covering the same or substantially the same subject matter.

[89] USPTO Patent Interference No. 106,048. Decisions on Motions 37 C.F.R. § 41.125(a).

[90] USPTO Patent Interference No. 106,048. Decisions on Motions 37 C.F.R. § 41.125(a).

[91] David Cyranoski and Heidi Ledford, 'Genome-Edited Baby Claim Provokes International Outcry (2018) 563 Nature 607, 608. See also Kevin Noonan, 'CRISPR Interference Parties Propose Motions' (*Patent Docs/Patent Law Weblog*, 1 August 2019) <www.patentdocs.org/2019/08/crispr-interference-parties-propose-motions.html > accessed 27 July 2021.

California's claims had been based on inventions made by Doudna, Charpentier and their collaborators.[92] As discussed above, their breakthrough research in 2012 had demonstrated that CRISPR-Cas9 can be used to cut and (possibly) edit DNA in vitro. However, the USPTO decided that this did not extend to editing genomes in advanced, or eukaryotic cells, and as such the Broad Institute's invention was novel and non-obvious having regard to the prior art.[93] UC Berkeley filed an appeal from the U.S. patent board's decision, but in 2018 that appeal was rejected by a US Court of Appeals.[94] Though the PTAB and the Court did not cancel or finally refuse any claims when terminating the interference, its decision triggered speculation that UC might eventually take US rights to use in *prokaryotes*, whereas the Broad Institute would take the lead in enforcing its US patents rights with regard to the use of CRISPR technologies in *eukaryotes*.[95]

However, in 2018, it turned out that UC Berkeley had initiated new USPTO interference procedures by filing new claims directed at the use of CRISPR-Cas9 in eukaryotic cells.[96] In order to decide which research group had provided the best evidence that the CRISPR-Cas9 technique works in eukaryotic cells, the U.S. Patent Office now conducted a more comprehensive comparison of the claims of competing inventors.[97] In September 10, 2020, the PTAB rejected UC Berkeley's arguments, and assigned UC Berkeley a filing date of January 28, 2013, whereas the PTAB assigned the Broad Institute a filing date of December 12, 2012.[98] Consequently, the Broad Institute managed to convince the PTAB that it has priority with regard to the – very significant – use of the CRISPR-Cas9

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[92] *Broad Institute, Inc. v. Regents of the University of California*, No. 106,048, (P.T.A.B., February 15, 2017).
[93] ibid.
[94] *Regents of the University of California v. Broad Institute, Inc.*, No. 2017-1907 (Fed. Cir. September 10, 2018).
[95] Duncan Matthews, 'Access to CRISPR Genome Editing Technologies: Patents, Human Rights and the Public Interest' (2020), Queen Mary School of Law Legal Studies Research Paper No. 332/2020, <https://ssrn.com/abstract=3595392> accessed 27 July 2021.
[96] See Vincent M de Grandpré and Felicia Lozon, 'Making Sense of the Battle for the CRISPR-Cas9 Patent Rights' (*Osler*, 15 March 2021) <www.osler.com/en/resources/critical-situations/2021/making-sense-of-the-battle-for-the-crispr-cas9-patent-rights> accessed 27 July 2021; Louis Lieto and others, 'Patent Trial and Appeal Board Hears Argument in CRISPR Patent Priority Dispute' (*JDSUPRA*, 21 May 2020), <www.jdsupra.com/legalnews/patent-trial-and-appeal-board-hears-96548/#3> accessed 27 July; "Methods and Compositions for RNA-Directed Target DNA Modification and for RNA-Directed Modulation of Transcription", U.S. Patent Application No. 15/981,807 (May 16, 2018), clm 156.
[97] ibid. Vincent M de Grandpré and Felicia Lozon citing Jon Cohen, 'The Latest Round in the CRISPR Patent Battle Has an Apparent Victor, but the Fight Continues" (11 September 2020) Science <www.sciencemag.org/news/2020/09/latest-round-crispr-patent-battle-has-apparent-victor-fight-continues> accessed 27 July 2021.
[98] ibid. Vincent M de Grandpré and Felicia Lozon citing *Regents of the University of California v. Broad Institute, Inc.*, No. 106,115, (P.T.A.B., September 10, 2020) 109-110; Kevin E Noonan, 'PTAB Decides Parties' Motions in CRISPR Interference' *(Patent Docs/Patent Law Weblog*, 11 September 2020) <www.patentdocs.org/2020/09/ptab-decides-parties-motions-in-crispr-interference.html> accessed 27 July 2021; Jon Cohen, 'The Latest Round in the CRISPR Patent Battle Has an Apparent Victor, but the Fight Continues" (11 September 2020) Science <www.sciencemag.org/news/2020/09/latest-round-crispr-patent-battle-has-apparent-victor-fight-continues> accessed 27 July 2021.

techniques in animal and plant cells. UC Berkeley, on the other hand, was assigned priority regarding claims directed to the use of the technique in other cells, such as bacterial cells.[99] Yet, this will still not settle the dispute. Instead, the decision requires UC Berkeley to provide more evidence that it was "first to invent" at a future interference hearing.[100] Many jurisdictions around the globe where patent applications claim priority from either the Broad Institute or the UC Berkeley patent applications are therefore awaiting the outcome of the U.S. proceedings.[101]

At the European Patent Office, however, the equivalent application by the Broad Institute for a European patent met a very different fate due to a procedural twist resulting in the Broad Institute's patent applications having a later date than UC Berkeley's. On 23 March 2018, the EPO Opposition Division (OD) found that its priority claim was not valid and revoked its patent for lack of novelty.[102] The case[103] was then referred to the EPO Board of Appeal (BoA).[104] The key issues before the BoA were whether the priority claim of the Broad Institute patent EP2771468 was valid and whether the EPO had the power to decide on entitlement to priority. The opponents to the Broad Institute argued successfully that the EPO is competent to decide on the priority issue and bound to do so by Article 87 of the European Patent Convention (EPC), and that the OD decision was in line with the large body of EPO case law on priority. The EPO case law provides that the right to claim priority from an earlier application, as set out in Article 87 EPC which itself is derived from Article 4 of the Paris Convention on the Protection of Industrial Property (1967), is afforded to the applicant of the earlier application and to no other party.

As such, the applicant (or applicants) must be the same as the original filing. The Broad Institute's European patent EP2771468 was based on a Patent Cooperation Treaty (PCT) filing (WO2014204729) claiming priority from a number of US provisional applications. One of the U.S. provisionals named an inventor-applicant who was not named on the

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[99] ibid. Vincent M de Grandpré and Felicia Lozon citing Jon Cohen, 'The Latest Round in the CRISPR Patent Battle Has an Apparent Victor, but the Fight Continues" (11 September 2020) Science <www.sciencemag.org/news/2020/09/latest-round-crispr-patent-battle-has-apparent-victor-fight-continues> accessed 27 July 2021.

[100] Jon Cohen, 'The Latest Round in the CRISPR Patent Battle Has an Apparent Victor, but the Fight Continues" (11 September 2020) Science <www.sciencemag.org/news/2020/09/latest-round-crispr-patent-battle-has-apparent-victor-fight-continues> accessed 27 July 2021.

[101] Vincent M de Grandpré and Felicia Lozon, 'Making Sense of the Battle for the CRISPR-Cas9 Patent Rights' (*Osler*, 15 March 2021) <www.osler.com/en/resources/critical-situations/2021/making-sense-of-the-battle-for-the-crispr-cas9-patent-rights> accessed 27 July 2021.

[102] See also Jacob Wested, Timo Minssen and Esther van Zimmeren,'Will the EPO's Enlarged Board of Appeal Hear the Broad's CRISPR Case?' (2018) Life Sciences Intellectual Property Review <www.lifesciencesipreview.com/article/will-the-epo-s-enlarged-board-hear-the-broad-s-crispr-case> accessed 27 July 2021.

[103] T 0844/18 CRISPR-Cas/BROAD INSTITUTE [16.1.2020], ECLI:EP:BA:2020:T084418.20200116.

[104] The EPO Boards of Appeal are, according to Article 21 EPC, 'responsible for the examination of appeals from decisions of the Receiving Section, the Examining Divisions and Opposition Divisions, and the Legal Division'.

PCT application.[105] The two earliest priority documents that the Broad Institute was seeking to rely on at the EPO from 12 December 2012 and 2 January 2013 named Luciano Marraffini of Rockefeller University as an inventor-applicant. Marraffini was not an applicant on the later patent and had not assigned priority rights to the Broad Institute. In fact, until mid-2017 the Broad Institute and Rockefeller University were in an inventorship dispute over a number of early CRISPR patents.[106] In January 2020, the '468 patent was thus revoked in view of an invalid priority claim.[107] Despite expectations that the BoA would refer questions on priority arising in the case to the EPO Enlarged Board of Appeal,[108] the BoA decided it could sufficiently answer all questions on priority. It therefore upheld the findings of the OD and dismissed the case on grounds that there was already a substantial and consistent body of EPO case law on the matter of priority under Article 87 EPC.[109]

In February 2020, the EPO's OD also dismissed objections to EP2800811 B1, which is held by the University of California (Berkeley) and University of Vienna, and the main inventors, Jennifer Doudna and Emmanuelle Charpentier, upholding the patent in its original form in May 2020.[110] Consequently, the UC Berkeley/University of Vienna group now holds all of the first-generation patents on CRISPR-Cas9 in Europe.

This outcome has also become an issue for the patent portfolio of companies that had filed CRISPR successor patents. While, so far, most proceedings did primarily focus on the question of priority and novelty, several of those follow-on patent applications face opposition with regard to the inventive step requirement. For example, Sigma-Aldrich, the

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[105] Duncan Matthews, 'Access to CRISPR Genome Editing Technologies: Patents, Human Rights and the Public Interest' (2020), Queen Mary School of Law Legal Studies Research Paper No. 332/2020, <https://ssrn.com/abstract=3595392> accessed 27 July 2021.

[106] Allen & Overy, 'Broad Institute CRISPR-Cas9 Patent Revoked in Europe' (*Allen & Overy*, 18 January 2018) <www.allenovery.com/en-gb/global/news-and-insights/publications/broad-institute-crispr-cas9-patent-revoked-in-europe> accessed 27 July 2021.

[107] See the EPO statement, 'Decision in case T 844/18 on the CRISPR gene editing technology', 17 January 2020, <www.epo.org/law-practice/case-law-appeals/communications/2020/20200117.html> accessed 27 July 2021.

[108] For further discussion, see Jacob Wested, Timo Minssen and Esther van Zimmeren, 'Will the EPO's Enlarged Board of Appeal Hear the Broad's CRISPR Case?' (2018) Life Sciences Intellectual Property Review <www.lifesciencesipreview.com/article/will-the-epo-s-enlarged-board-hear-the-broad-s-crispr-case> accessed 27 July 2021.

[109] The full reasoning behind the January 2020 decision had been made available first in November 2020, see Decision in case T 844/18 on the CRISPR gene editing technology, see T 0844/18 of 16 January 2020, <http://documents.epo.org/projects/babylon/eponet.nsf/0/22848DBA6784C883C1258617004D48BB/$File/0844.18.3308(decision).pdf> accessed 27 July 2021.

[110] See EP2800811 - Methods and Compositions for RNA-Directed Target DNA Modification and for RNA-Directed Modulation of Transcription, <https://register.epo.org/application?number=EP13793997&lng=en&tab=main> accessed 27 July 2020. See further Amy Sandys, 'EPO Revokes First Sigma-Aldrich CRISPR Patent for Lack of Inventive Step' (*Juve Patent,* 19 March 2021) <www.juve-patent.com/news-and-stories/cases/epo-revokes-first-sigma-aldrich-crispr-patent-for-lack-of-inventive-step/> accessed 27 July 2021.

Broad Institute, and South Korean company Toolgen, have filed European patent applications directed to the further development of the original CRISPR/Cas technology and have transferred it to human cells. However, the EPO revoked Sigma-Aldrich's EP3138910 B1[111] for lack of inventive step over the original Doudna/Charpentier published work.[112] In addition, the Broad Institute is facing further oppositions to EP3009511, which is directed to CRISPR-Cpf1 (now called Cas12a) systems.[113]

2.3. The TRIPS Agreement and its implementation

2.3.1. TRIPS Flexibilities

Debate around the grant of patents, and disputes around validity, can also arise on other bases. Patent laws around the globe contain both pre-grant limitations on what may be protected by a patent and post-grant limits to the protection conferred by a patent. Legal terminology may vary, but most commonly these are described in statutes, case-law and legal literature as either exclusions, exceptions or limitations.[114] These are collectively referred to as TRIPS flexibilities and allow national patent laws to contain public governance mechanisms concerning technological innovation. Pre-grant limitations can be an effective instrument for public governance, e.g. by delimiting the object of a patent (inventions) and excluding certain subject-matter from such a concept (exclusions) or determining that certain types of inventions cannot obtain patent protection (exceptions). Post-grant measures may limit the reach of patents (limitations), by exempting certain activities (e.g. research exemptions) or persons from the scope of patent protection (e.g. liability exemptions for medical practitioners) or restricting the patent owner's contractual freedom concerning the patent as an object of property (e.g. compulsory licenses).

2.3.2 '*Ordre public'* and morality exceptions

The TRIPS Agreement in Article 27.2 and 27.3 explicitly allows WTO Members to exclude certain inventions from patentability if justified by, in essence, overriding societal

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[111] See EP 3138910 B1 - CRISPR-Based genome Modification and Regulation <https://data.epo.org/gpi/EP3138910B1-CRISPR-BASED-GENOME-MODIFICATION-AND-REGULATION> accessed 27 July 2021.

[112] See Amy Sandys, 'EPO Revokes First Sigma-Aldrich CRISPR Patent for Lack of Inventive Step' (*Juve Patent,* 19 March 2021) <www.juve-patent.com/news-and-stories/cases/epo-revokes-first-sigma-aldrich-crispr-patent-for-lack-of-inventive-step/> accessed 27 July 2021, adding: "The EPO has also issued two preliminary opinions along with the summons for two further upcoming cases. Both deny the parties have inventive step over the initial publication. The EPO will hear the first case, involving applicant Toolgen and EP 2 912 175 B1, from 22 – 25 June 2021. The second case, which involves prolific CRISPR patent applicant the Broad Institute, is scheduled to be heard on 16 and 17 November 2021. The latter case involves EP 29 21 557 A1."

[113] Michael Stramiello, 'Surveying the CRISPR Patent War' (*Law360*, 3 May 2018) <https://webstorage.paulhastings.com/Documents/Default%20Library/surveying-the-crispr-patent-war---law360.pdf> accessed 27 July 2021.

[114] When providing national or regional examples, the original terminology will be employed.

interest,[115] 'including to protect human, animal or plant life or health or to avoid serious prejudice to the environment'.[116] Specifically, Article 27.2 permits WTO members to "exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect 'ordre public' or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law".

Although, TRIPS does not provide for a definition of '*ordre public'* and morality, it expressly includes within this the concept the protection of life and health. In WTO Dispute Settlement Panel Report in *Canada – Patent Protection of Pharmaceutical Products*, the Panel confirmed that Article 8.1 of the TRIPS Agreement (in the context of the prohibition on discrimination as to the field of technology contained in Article 27.1 of TRIPS) "does not limit the ability to target certain products in dealing with certain of the important national policies referred to [in Article 8.1]. It would appear therefore, that there exists considerable scope for WTO Members to include in national legislation exclusions based on the measures necessary to protect public health… and to promote the public interest…" under Article 27.2 of TRIPS.[117]

It should also be emphasised that Article 8.1 and 27.2 of TRIPS does not impose patentability exceptions. It merely provides member states with options or flexibilities concerning patentability and its interface with public policy and ethical issues surrounding technology. It is a question for each member state to decide if and how to legislate in this matter, and whether to enact or develop via case-law '*ordre public'* and morality exceptions to patentability.

[115] See also UNCTAD-ICTSD Project on IPRs and Sustainable Development, *Resource Book on TRIPS and Development* (Cambridge University Press 2005) 378.

[116] Article 27.2 TRIPS Agreement, World Trade Organization, Agreement on Trade-Related Aspects of Intellectual Property Rights (as amended on 23 January 2017), Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, signed in Marrakesh, Morocco on 15 April 1994 <www.wto.org/english/docs_e/legal_e/31bis_trips_01_e.htm> accessed 27 July 2021.

[117] WTO, Canada – Patent Protection of Pharmaceutical Products, Report of the Panel, WT/DS114/R, 17 March 2000, paragraph 7.92, <www.wto.org/english/tratop_e/dispu_e/7428d.pdf> accessed 27 July 2021.

Box 1. Countries with national laws providing exceptions from patentability on the ground of commercial exploitation being contrary to *ordre public* or morality include:

Austria, Barbados, Belgium, Belize, Bolivia, Bosnia and Herzegovina, Bulgaria, Chile, he People's Republic of China, Hong Kong China, Colombia, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Dominica, Dominican Republic, Ecuador, Egypt, El Salvador, Estonia, Finland, France, Germany, Ghana, Greece, Guatemala, Hungary, Iceland, India, Indonesia, Ireland, Italy, Japan, Jordan, Kazakhstan, Kenya, Kyrgyz Republic, Latvia, Liechtenstein, Lithuania, Luxembourg, Madagascar, Malaysia, Malta, Mauritius, Mexico, Moldova, Morocco, Mozambique, Netherlands, New Zealand, Nicaragua, Nigeria, Norway, Republic of North Macedonia, Oman, Pakistan, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Poland, Portugal, Republic of Korea, Romania, Russian Federation, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Tajikistan, Thailand, Trinidad and Tobago, Tunisia, Turkey and United Kingdom, Uruguay, Uzbekistan, Zambia.

Source: WIPO Standing Committee of the Law of Patents (SCP), April 2020.[118]

Exceptions from patentability on the ground of commercial exploitation being contrary to '*ordre public*' or morality can be found in some regional patent treaties,[119] including the African Intellectual Property Organization (OAPI),[120] the Eurasian Patent Organization (EAPO)[121] and the EPO.[122] Also the national law of a large number of WTO members

[118] World Intellectual Property Organization, 'Certain Aspects of National/Regional Patent Laws', <www.wipo.int/export/sites/www/scp/en/national_laws/exclusions.pdf > accessed 27 July 2021.

[119] These implement and in some cases supplement the TRIPS Agreement including for example making use of the flexibilities allowed by Article 8 and further developed in Articles 27,30 and 31 concerning patent exclusions, exceptions and limitations. World Trade Organization, Agreement on Trade-Related Aspects of Intellectual Property Rights (as amended on 23 January 2017), Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, signed in Marrakesh, Morocco on 15 April 1994 <www.wto.org/english/docs_e/legal_e/31bis_trips_01_e.htm> accessed 27 July 2021.

[120] Section 3, Article 10 (j), Protocol on Patents and Industrial Designs within the framework of the African Regional Intellectual Property Organization (ARIPO), adopted on December 10, 1982, at Harare (Zimbabwe), and amended by the Administrative Council of ARIPO on December 11, 1987, April 27, 1994, November 28, 1997, May 26, 1998, November 26, 1999, November 30, 2001, November 21, 2003, November 24, 2006, November 25, 2013, November 17, 2015, December 5, 2016, November 22, 2017, November 23, 2018 and November 20, 2019,
<www.aripo.org/wp-content/uploads/2020/01/Harare-Protocol-2020-Edition-1.pdf> accessed 27 July 2021.

[121] Rule 3 (4), Patent Regulations under the Eurasian Patent Convention Adopted by the Administrative Council of the Eurasian Patent Organization (EAPO AC) at its second (1st ordinary) session on December 1, 1995, with the amendments and addenda adopted by EAPO AC up to its thirty-sixth (27th ordinary) session on September 10-11, 2020 (non-official English translation)
<www.eapo.org/en/documents/norm/instr2020_eng.pdf> accessed 27 July 2021.

[122] Article 53 (a) EPC, <www.epo.org/law-practice/legal-texts/html/epc/2016/e/ar53.html> accessed 27 July 2021.

(see Box 1) contains specific '*ordre public*' and morality provisions, conceptualised in the context of local legal traditions. For example,[123] under the Patent Law of the People's Republic of China Article 5 sets out that "Patent rights shall not be granted for invention-creations that violate the law or social ethics, or harm public interests".[124] As regards the interpretation of Article 5 of the Patent Law of the People's Republic of China, it should be noted that already the Patent Examination Guidelines of the State Intellectual Property Office of the People's Republic of China (SIPO), which in 2018 has been replaced by CNIPA (the China National Intellectual Property Administration), explained in a detailed way the meaning of the locutions "social morality" and "public interest". They provided, in particular, a list of examples of inventions which could be deemed contrary to "social morality", such as "an artificial sexual organ or its substitute not designed for medical use, *a process for modifying the genetic identity of the human being's germ line or use of human embryos for industrial or commercial purposes*, a process for cloning human beings, a process for modifying the genetic identity of animals which is apt to cause suffering to the animals, as long as it has no substantial value for the treatment of human beings or animals".[125] However, it should be emphasised that not all WTO members have implemented in their respective national patent laws '*ordre public'* and morality exceptions, and among those that have, application and enforcement practices may vary considerably.[126]

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[123] See Alice Yuen-Ting Wong and Aurélie Mahalatchimy, 'Human Stem Cells Patents - Emerging Issues and Challenges in Europe, United States, China, and Japan' (2018) 21 The Journal of World Intellectual Property 326, 338.

[124] Article 5, Patent Law of the People's Republic of China as amended to the Decision of 17 October 2020 of the Standing Committee of the National People's Congress on Amending the Patent Law of the People's Republic of China, <https://wipolex.wipo.int/en/text/582995> accessed 27 July 2021. The English non official translation of Article 5 Patent Law of the People's Republic of Chinas is available at: Patent Law of the People's Republic of China (2021) 1 China Patents and Trademarks 82, <www.cpahkltd.com/UploadFiles/20201222110401200.pdf> accessed 27 July 2021.

[125] Part II, Chapter, 1 Section 3.2 Inventions-Creations against Social Morality, SIPO's Patent Examination Guidelines, <www.wipo.int/edocs/lexdocs/laws/en/cn/cn192en.pdf> accessed 27 July 2021, 119. Emphasis added. See Bu Yuanishi, 'Prerequisites for Protection' in Stefan Luginbuehl and Peter Ganea (eds), *Patent Law in China* (Edward Elgar 2014) 43, 44.

The Chinese Patent Examination Guidelines have been recently revised and the new CNIPA's Patent Examination Guidelines came into force on 15 January 2021 <www.cnipa.gov.cn/art/2015/1/9/art_99_28237.html> accessed 27 July 2021. However, the amendments did not involve this specific part of the Patent Examination Guidelines and the examples set out in Section 3.1.2 regarding Inventions-Creations against Social Morality are identical to the ones set forth in the former Part II, Chapter, 1 Section 3.2 Inventions-Creations against Social Morality of SIPO's Patent Examination Guidelines.

See Jennifer Che, Yolanda Wang and Sally Yu, 'China's Newest Examination Guidelines: Novelty and Inventive Step for Compounds (Part II)' (*China Patent Strategy/ Eagle IP*, 29 April 2021) <https://chinapatentstrategy.com/chinas-examination-guidelines-novelty-inventive-step-chemical-compounds-part-ii/> accessed 27 July 2021.

[126] Timo Minssen, 'Patenting Human Genes in Europe - and How It Compares to the US and Australia' in Duncan Matthews and Herbert Zech (eds), *Research Handbook on Intellectual Property and the Life Sciences* (Edward Elgar 2017) 26. See Ana Nordberg and Timo Minssen, 'A 'Ray of Hope' for European Stem Cell Patents or 'Out of the Smog into the Fog'?: An Analysis of Recent European Case Law and How It Compares to the US' (2016) 47(2) IIC 138.

2.3.2.1. Developments in the USA

In the US it is generally understood that there are no enforceable statutory provisions corresponding to '*ordre public'* and morality exceptions to patentability. Most jurisprudential activity around determining the boundaries of subject-matter eligibility corresponds to a prohibition on patenting natural laws, products, phenomena or abstract ideas.[127] The U.S. Supreme Court decision in *Diamond v. Chakrabarty* (1980)[128] clarified that whether an invention embraces living matter is irrelevant to the issue of patent eligibility, with the seminal conclusion that statutory subject matter under section 101 includes "anything under the sun that is made by man".

More recent decisions have introduced a stricter approach to patent eligibility. In *Bilski v. Kappos* (2010)[129] the Supreme Court addressed the contested patent eligibility of method patents in general. Section 101 of the patent act enumerates the different types of claims allowed: "process, machine, manufacture, or composition of matter".[130] The Court rejected a categorical exclusion from patent eligibility of business methods, while also rejecting the machine-or-transformation test. In *Mayo v. Prometheus* (2012), the US Supreme Court focused again on Section 101 and its implicit exception that excludes patents on laws of nature, natural phenomena, and abstract ideas, here concerning a '*medical method'*.[131] The matter was again raised in *Association for Molecular Pathology v. Myriad Genetics* (2013), concerning the controversial patents on the BRCA1 and BRCA2 genes.[132] Here the US Supreme Court decided on the patent eligibility of isolated genes concluding that a naturally occurring DNA segment was a product of nature and not patent eligible under 35 U.S.C. § 101 merely because it was isolated, but cDNA was patent eligible because it was not naturally occurring. In *Alice Corp. v. CLS Bank International* (2014),[133] although not a life sciences case, the deliberations of the Supreme Court were also instructive because the court discussed the boundaries between non-

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[127] Historical authors refer to this approach as the "moral utility" doctrine. See Margo A Bagley, 'Patent First, Ask Questions Later: Morality and Biotechnology in Patent Law' (2003) 45(2) William and Mary Law Review 469.

[128] *Diamond v. Chakrabarty* 447 U.S. 303 (1980); 206 USPQ 193 (The Supreme Court of the United States).

[129] *Bilski v Kappos* 130 s. Ct. 3218; 177 L.Ed.2d 792 (2010).

[130] 35 U.S.C. § 101, <https://uscode.house.gov/view.xhtml?path=/prelim@title35/part2/chapter10&edition=prelim> accessed 27 July 2021.

[131] *Mayo Collaborative Servs. v. Prometheus Labs, Inc*., 132 S. Ct. 1289 (2012). See Timo Minssen and David Nilsson, 'The US Supreme Court in Mayo v. Prometheus - Taking the Fire from or to Biotechnology and Personalized Medicine?' (2012) 2(4) Queen Mary Journal of Intellectual Property 376.

[132] *Association for Molecular Pathology, et al. v. Myriad Genetics, Inc.* 569 U.S. 576, 133 S. Ct. 2107 (2013). An account of the developments leading to the Myriad decision is provided by Robert M Schwartz and Timo Minssen, 'Life after Myriad: The Uncertain Future of Patenting Biomedical Innovation & Personalized Medicine in an International Context' (2015) 3 189; Esther van Zimmeren and others, 'The BRCA Patent Controversies: An International Review of Patent Disputes' in Sahra Gibbon and others (eds) *Breast Cancer Gene Research and Medical Practices: Transnational Perspectives in the Time of BRCA* (Routledge 2014) 151. For a discussion of the ethical issues and gene patentability in this context see Aisling McMahon, ''Gene Patents and the Marginalisation of Ethical Issues' (2019) 41(10) European Intellectual Property Review 608.

[133] *Alice Corp. v. CLS Bank International,* 573 U.S. 208 (2014).

patentable abstract ideas and patent eligibility of implementations of ideas - in this case a software patent.[134]

These decisions show that the US system addresses many of the public policy concerns and in a general and systematic manner through the application of patent eligibility standards. In contrast, other jurisdictions address such concerns typically through more specific national and supra-national rules based on the exceptions from patentability under art 27.2 TRIPS. Recent developments in Europe illustrate this approach.

2.3.2.2. Developments in Europe

Patentability prohibitions based on '*ordre public'* and morality have a long tradition in national laws and already existed in several jurisdictions in the nineteenth century.[135] Historically, the origin of these provisions pre-dates both the TRIPS Agreement and the EPC and other regional treaties. Currently, the general '*ordre public*' and morality clause is prescribed in Article 53.a of the EPC in terms very close to those of Art 27.2 TRIPS.[136]

The EPC does not contain a statutory definition of '*ordre public'* and morality, however the implementing regulations to the EPC[137] contain some examples of inventions that are considered to fall under the scope of the provision. These regulations incorporate EU rules of the Biotechnology Directive,[138] indirectly extending their scope of territorial application to those member states of the EPO which are not part of the EU. Although the EPO, as an international organisation based on an international treaty – the EPC – is independent from and not subject to the treaties and legislation of the EU, the EPO Administrative Council adopted all the articles of the Biotechnology Directive into its own legal order via the implementing rules of the EPC.[139]

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[134] Regarding the impact of the *Alice* decision on biotechnology patents, see Mateo Aboy and others, 'How Does Emerging Patent Case Law in the US and Europe Affect Precision Medicine?' (2019) 37(10) Nature Biotechnology 1118.

[135] See Lionel Bently, Brad Sherman and others, 'Exclusions from Patentability and Exceptions and Limitations to Patentees' Rights', (WIPO Standing Committee on the Law of Patents SCP/15/3 Annex I) (2010)).

[136] Article 53(a) EPC 2000 reads as follows: 'European patent shall not be granted in respect of: (a) inventions the commercial exploitation of which would be contrary to 'ordre public' or morality; such 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.'

[137] Implementing Regulations to the Convention on the Grant of European Patents of 5 October 1973 as adopted by decision of the Administrative Council of the European Patent Organisation of 7 December 2006 and as last amended by decision of the Administrative Council of the European Patent Organisation of 15 December 2020.

[138] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions [1998] OJ L213/13 (Biotechnology Directive).

[139] The key articles 5 and 6 of the Biotechnology Directive are included in Rules 28 and 29 of the Implementing Regulations to the Convention on the Grant of European Patents. Administrative Council Decision, OJ EPO 7/1999, 437.

Applying these provisions has been a source of controversy and academic debate,[140] as this involves ethical normative decisions – determining what is contrary to '*ordre public'* or morality, to be made by administrative institutions (the EPO or national patent offices). These are considered by many to lack the structure, technical expertise, institutional culture of transparency and accountability, or indeed a democratic mandate to assume such a role.[141] Likewise, the role of the CJEU and national courts in determining standards of morality for patent law purposes has been questioned.[142]

The Biotechnology Directive, enacted by the EU in 1998 after a decade-long legislative process, was an attempt to create greater certainty regarding both patent eligibility and patentability exclusions and exceptions applicable to the, then emerging, biotechnology field. It contains rules providing distinction between inventions and non-patentable discoveries, as well as examples of what inventions might not fall under the scope of the '*ordre public'* or morality exception. Article 5 of the Biotechnology Directive focuses on the human body which, at various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions but a mere discovery of a naturally occurring

[140] For some background see: Ana Nordberg, 'Patents, Morality and Biomedical Innovation in Europe: Historical Overview, Current Debates on Stem Cells, Gene Editing and AI, and de Lege Ferenda Reflections' in Daniel Gervais (ed), *Fairness, Morality and Ordre Public* (Edward Elgar 2020) 243; EU Commission Expert Group on the development and implications of patent law in the field of biotechnology and genetic engineering, 'Report on patents in the field of human stem cells of the Expert Group on the development implications of patent law in the field of biotechnology and genetic engineering' (2016) <https://ec.europa.eu/growth/industry/policy/intellectual-property/patents/biotechnological-inventions_en> accessed 27 July 2021; Sigrid Sterckx and Julian Cockbain *Exclusions from Patentability: How Far Has the European Patent Office Eroded Boundaries* (Cambridge University Press 2012) 75; Joseph Straus, 'Ordre Public and Morality Issues in Patent Eligibility' in Toshiko Takenaka (ed) *Intellectual Property in Common Law and Civil Law* (Edward Elgar 2013) 19, 29; Åsa Hellstadius, 'A Quest for Clarity: Reconstructing Standards for the Patent Law Morality Exclusion' (PhD thesis, Stockholm University 2015); J Hitchcock J and C Sousa e Brito, 'Case Comment: Should Patents Determine When Life Begins?' (2014) 36(6) European Intellectual Property Review 390; Geertrui Van Overwalle, 'Legal and Ethical Aspects of Bio-patenting: Critical Analysis of the EU Biotechnology Directive' in Peter Drahos (ed) *Death of Patents, Perspectives on Intellectual Property Law and Policy*, vol 11 (Lawtext Publishing 2005) 212; Aisling McMahon, 'Patents, Governance and Control: Ethics and the Patentability of Novel Beings and Advanced Biotechnologies in Europe' (2021) 30(1) Cambridge Quarterly of Healthcare Ethics 529.

[141] Justine Pila, 'Adapting the *Ordre Public* and Morality Exclusion of European Patent Law to Accommodate Emerging Technologies' (2020) 38 *Nature Biotechnology* 555; Ana Nordberg, 'Patents, Morality and Biomedical Innovation in Europe: Historical Overview, Current Debates on Stem Cells, Gene Editing and AI, and de Lege Ferenda Reflections' in Daniel J Gervais (ed), *Fairness, Morality and Ordre Public in Intellectual Property* (Edward Elgar 2020) 243; Ingrid Schneider, (2016) 'Dissenting Opinion, in Annex B5 to Report on patents in the field of human stem cells of the Expert Group on the development implications of patent law in the field of biotechnology and genetic engineering' (E02973), <www.biogum.uni-hamburg.de/3pdf-med/dissenting-opinion-ingrid-schneider-stem-cell-report.pdf> accessed 27 July 2021; Paul Torremans, 'The Construction of the Directive's Moral Exclusions under the EPC' in Aurora Plomer and Paul Torremans (eds), *Embryonic Stem Cells Patents* (OUP 2009) 162, arguing that a unified concept of European ethics does not exist; Adrian M Viens, 'Morality Provisions in Law Concerning Commercialization of Human Embryos and Stem Cells' in Aurora Plomer and Paul Torremans (eds), *Embryonic Stem Cells Patents* (OUP 2009) 111, observing that a definition of morality is always one of cultural normative relativism.

[142] See with further references, Ana Nordberg, 'Legal Method and Legal interpretation in International Intellectual Property Law: Pluralism or Systemic Coherence' in Susy Frankel (ed), *Is Intellectual Property Pluralism Functional?* (Edgar Elgar 2019) 96.

element. Nevertheless, Article 5 goes on to state that an element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to a natural element, provided that the industrial application of a sequence or a partial sequence of a gene is disclosed in the patent application. On its turn, Article 6.2 sets out a non-exhaustive list of examples of biotechnological inventions that are excluded from patentability on '*ordre public*' and morality grounds, including: (a) "processes for cloning human beings"; (b) "processes for modifying the germ line genetic identity of human beings"; and (c) "uses of human embryos for industrial or commercial purposes".

It is important to again emphasise that the EPO is not an institution of the European Union and not all of its members are EU member states. Therefore, EU directives and CJEU decisions cannot be invoked nor are they legally binding for the EPO, even if the BoA may decide to find the jurisprudence persuasive and the institutional practice has been to incorporate CJEU patent decisions in the guidelines for examination. These are two parallel systems that are not always fully aligned, and both the EPO BoA and the CJEU have established interpretative guidance through a number of high-profile cases. The *OncoMouse* case[143] established a balancing test weighing animal suffering against the therapeutic value of the invention under consideration.[144] In *Relaxin*,[145] it was instead suggested that the main criterion for morality assessment rested on whether the invention is so abhorrent to the public that it would seem inconceivable[146]. While in *Plant cells*,[147] it was stated that 'the concept of "*ordre public*" covers the protection of public security and the physical integrity of individuals as part of society',[148] and that the concept of morality is related to the accepted norms which are deeply rooted in the culture inherent in European society and civilisation.[149] The specific criteria and acceptable evidentiary sources for deciding the actual substantive content of what constitutes an accepted norm that is deeply rooted in European society remains mostly undetermined. In *Transgenic Animal* (which was issued after the EU Biotechnology Directive was adopted) it was stated that no single definition of morality based on, for instance, economic or religious principles, represents the content of an accepted standard in European culture.[150]

The EPO found that the legislature had made morality part of the EPC[151] in the context of innovation linked ultimately with embryos and declined to grant patents.[152] Any genome

[143] T 19/90 Harvard/*Onco-mouse* [03.10.1990] OJ EPO 1990, 476.
[144] ibid, reasons 5.
[145] Decision of the EPO Opposition Division, Howard Florey Institute/*Relaxin* [08.12.1994] OJ EPO 1995, 388 and T 272/95 Howard Florey Institute/*Relaxin* [23.10.2002] unpublished.
[146] Howard Florey Institute/*Relaxin* [08.12.1994] reasons 6.2.1.
[147] T 356/93 Plant Genetic Systems/*Plant cells* [21.02.1995] OJ EPO 1995, 545.
[148] ibid, reasons 5.
[149] ibid.
[150] T 315/03 HARVARD/*Transgenic Animal* [06.07.2004] OJ EPO 2005, 246.
[151] See Amanda Warren-Jones, 'Finding a "Common Morality Codex" for Biotech - a Question of Substance' (2008) 39(6) IIC 638.
[152] WARF/*Embryonic Stem Cells* [2009] EPOR 15, 143 para 41, and the issue had been raised of a genuine European ordre public, 135, para 7 and consideration in Aurora Plomer and others, 'Challenges to Human

editing invention that implies at some point the destruction of an embryo is not patentable. An invention that uses hESC's is only patentable if stem cell lines were obtained from parthenotes. According to the CJEU in *Brüstle*, this limitation even applies if the destruction occurred at an undetermined historical moment and does not form part of the invention, as described in the claims.[153] The CJEU*[154]* focused on establishing the meaning of embryo within the Directive and did not engage with wider questions of human dignity and morality, despite the opinion of the Advocate General in this case.[155] The *Brüstle* case, later adopted by the EPO concerning patentability of human stem cells, contrasts with the EPO less restrictive approach to patenting regarding genetic innovation in earlier decisions concerning animals in H*arvard/Onco-mouse*[156] when it balanced the impact on the animals with the longer term expected benefit for humans.

When considering environmental issues in *Plant Genetic Systems,*[157] the EPO BoA concluded that in order to establish that a commercial exploitation would be contrary to public order and morality on the basis of serious prejudice to the environment (one of the bases specifically set out in TRIPS) the threat to the environment needed to be sufficiently substantiated at the time of the EPO decision.[158] This approach was seen again in *Novartis II transgenic plant*,[159] when the EPO was reluctant to engage with the economic and social consequences of patenting for subsistence farmers.[160] This is a rather narrow view, and it has been criticized by not taking into account the uncertainty which may arise from disruptive and radical innovation[161] and the precautionary principle (see below 2.3.4).

Modifying the germline genetic identity of human beings is covered by the morality patentability exception under the EU Biotechnology Directive and corresponding Rule 28.1.b in the EPC Implementing Regulations. This modification is also, outside patent laws, expressly prohibited in several jurisdictions and heavily regulated in others.[162] Rule

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Embryonic Stem Cell Patents' (2008) 2(1) Cell Stem Cell 13. Cf. with other jurisdictions, e.g. the USA where equivalent patents were granted.

[153] Ana Nordberg and Timo Minssen, 'A 'Ray of Hope' for European Stem Cell Patents or 'Out of the Smog into the Fog'?: An Analysis of Recent European Case Law and How It Compares to the US' (2016) 47(2) IIC 138.

[154] Case C-34/10 *Oliver Brüstle v Greenpeace e.V* [2011] OJ C 362/5 Judgment of the Court (Grand Chamber) of 18th of October 2011.

[155] Opinion of Advocate General Bot of 10 March 2011, Case C-34/10 O*liver Brüstle v Greenpeace e V*.

[156] T 19/90 Harvard/*Onco-mouse* [03.10.1990] OJ EPO 1990, 476 (and n 125 above); Deryck Beyleveld and Roger Brownsword, *Mice, Morality and Patents: the Oncomouse Application and Article 53a of the European Patent Convention* (Intellectual Property Institute 1993, also considered in Amanda Warren-Jones, 'Finding a "Common Morality Codex" for Biotech - a Question of Substance' (2008) 39(6) IIC 638; Angelica Bonfanti, 'Environmental Risk in Biotech Patent Disputes' (2012) 3(1) EJRR 47, 49-51.

[157] T 356/93 Plant Genetic Systems/*Plant cells* [21.02.1995] OJ EPO 1995, 545 (and n 145).

[158] See comment and criticism in Estelle Derclaye, 'Should Patent Law Help Cool the Planet? An Enquiry from the Point of View of Environmental Law Part 2' (2009) 31 EIPR 227, 230; Angelica Bonfanti, 'Environmental Risk in Biotech Patent Disputes' (2012) 3(1) E.J.R.R. 47.

[159] G 1/98/NOVARTIS II/*Transgenic plant* [20.12.1999] OJ EPO 2000, 111.

[160] Justine Pila, 'Adapting the *Ordre Public* and Morality Exclusion of European Patent Law to Accommodate Emerging Technologies' (2020) 38 *Nature Biotechnology* 555.

[161] ibid.

[162] Concerning Europe, see, for example, the restriction imposed by Article 13, Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the

28.1.b explicitly includes in the morality exception 'processes for modifying the germ line genetic identity of human beings'. Product claims are not excluded directly, making EPO decisions on the morality of the invention depend on the type of claim used. While process claims are covered directly by the letter of the law, product claims are evaluated under the general morality clause on a case-by-case basis.[163] Likewise somatic editing interventions fall completely outside the scope of Rule 28.1.b. However, these interventions will also still be subject to an assessment of moral conformity under the general '*ordre public'* and morality clause. These interventions may be controversial as well, as for example there might be objections if these interventions are intended for other than medical purposes, such as doping in sports, academia or work, aesthetic and self-expression interventions (such as beauty treatments and extreme body modifications) or generally any type of induced human evolutionary purposes and other interventions commonly debated in bioethics as human enhancement.[164]

There are, however, considerable legal discussions on how to interpret and apply these rules, since the legal text of the directive is built on relatively vague and undetermined autonomous concepts of EU law that require clarification. Under a literal interpretation, all interventions that result in modifications being passed down to descendants will be excluded from patentability, even if the main purpose of the intervention is therapeutic and not in any way connected with eugenic purposes. However, EU law and ergo the biotechnology directive, is traditionally not interpreted under its literal meaning, but following a teleological interpretation method.[165] It has been argued that in such cases a less strict interpretation would be reasonable as a contextual interpretation would allow patents on in vitro methods where the main purpose is therapeutic.[166]

Moreover, recital 42 of the EU Biotechnology Directive, which has interpretative value, affirms that the germline 'exclusion does not affect inventions for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it'. Following from the doctrine of the CJEU in *Brüstle* considered above and *ISCC,* a broad interpretation of the legal concept of embryo was adopted, and therefore a therapeutic intervention at the blastocyst stage can be considered a therapeutic intervention in an embryo. Therefore, it

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Application of Biology and Medicine: Convention on Human Rights and Biomedicine (CETS no. 164). Only 28 countries have ratified, those who did not ratify include the EU as an institution and the following EPO member states: Ireland, Italy, the Netherlands, Poland, Sweden and the UK.

[163] Ana Nordberg, 'Patents, Morality and Biomedical Innovation in Europe: Historical Overview, Current Debates on Stem Cells, Gene Editing and AI, and de Lege Ferenda Reflections' in Daniel J Gervais (ed), *Fairness, Morality and Ordre Public in Intellectual Property* (Edward Elgar 2020) 243.

[164] Ana Nordberg, 'Defining Human Enhancement: Towards a Foundational Conceptual Tool for Enhancement Law' (2017) 25(3) Journal of Law Information & Science 1; Ana Nordberg, 'Human Enhancement from Ethical Interrogations to Legal (Un)certainty' in Tana Pistorius (ed) *Intellectual Property Perspectives on the Regulation of New Technologies* (Edward Elgar 2018) 54.

[165] Concerning legal interpretation and construction of international patent law, see also with further references, Ana Nordberg, 'Legal Method and Legal Interpretation in International Intellectual Property Law: Pluralism or Systemic Coherence' in Susy Frankel (ed) *Is Intellectual Property Pluralism Functional?* (Edgar Elgar 2019) 96.

[166] Ana Nordberg and others, 'Cutting Edges and Weaving Threads in the Gene Editing (*Я*)evolution: Reconciling Scientific Progress with Legal, Ethical, and Social Concerns' (2018) 5(1) Journal of Law and the Biosciences 35; Ana Nordberg and others, 'Regulating Germline Editing in Assisted Reproductive Technology: An EU Cross-Disciplinary Perspective' (2020) 3(1) Bioethics 16, with further references.

can be argued that gene editing for a therapeutic purpose is patentable, even if it might also constitute germline editing.[167] Likewise, following such reasoning but now *a contrario*, methods for germline editing would be patentable as long as not able to result in heritable modifications to a human being, meaning for example to be applied for research purposes in parthenotes which are not considered in EU law capable of developing into a human being and thus not covered by the prohibition in Article 6.2 Biotechnology Directive/ Rule 28.1.b EPC.

The European patent system has also used other governance tools to assess and manage what types of inventions should be excluded from patentability on grounds that they are, broadly speaking, socially undesirable and/or violate human dignity. Rather that relying on adversarial procedures (refusals and appeals) EPO administrative procedural rules and praxis on patent processing and examination allow the EPO examining division to regularly invite applicants to voluntarily introduce amendments to claims – known as disclaimers – explicitly excluding from the claims the use of a process for modifying the germline genetic identity of human beings.[168] Disclaimers have been added to genome editing-related patent applications such as "non-human", "human germline not modified" or "wherein the cells are not germ cells".[169] European patent claims have also been allowed to the "composition" or "vector system".[170] These procedural aspects of the patent examination process are particularly important for public governance. Moreover, they were relevant for the European Academies Statement on Patent-Related Aspects of CRISPR-Cas Technology[171] issued in 2016, which concluded that the patent granting practice of the EPO is fit for purpose and flexible enough to take account of future regulatory developments related to genome editing technology.

Although challenges remain and the search for balance runs throughout patent law, it has been argued that pursuing limitations and disclaimers, or refusal to grant, may start a chain reaction leading to an overall reduction of incentives to innovate and invest in controversial areas for R&D.[172] However, given that most technologies have dual or

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[167] Ana Nordberg, 'Patents, Morality and Biomedical Innovation in Europe: Historical Overview, Current Debates on Stem Cells, Gene Editing and AI, and de Lege Ferenda Reflections' in Daniel J Gervais (ed), *Fairness, Morality and Ordre Public in Intellectual Property* (Edward Elgar 2020) 243.

[168] Ingrid Schneider, 'Patent Governance, Ethics and Democracy: How Transparency and Accountability Norms Are Challenged by Patents on Stem Cells, Gametes and Genome Editing' in Thomas C Berg, Roman Cholij and Simon Ravenscroft (eds), *Patents on Life: Religious, Moral and Social Justice Aspects of Biotechnology and Intellectual Property* (Cambridge University Press 2019), 263.

[169] See also Schneider ibid.

[170] Examples include the European Patents EP 2800811 (UC Berkeley) and EP 2771468 (Broad Institute) with similar amended claim language, i.e. "provided that said method is not a method of modifying the germline genetic identity of a human being" (in the case of the Broad '468 EP, this wording being upheld during Oral Proceedings at the EPO, 5-7 February 2020, even if the patent was ultimately revoked on other grounds, as explained in section 2.2.2. above).

[171] ALLEA, Statement on Patent Related Aspects of CRISPR-Cas Technology, 18 July 2016,<https://allea.org/allea-releases-statement-patent-related-aspects-crispr-cas-technology/> accessed 27 July 2021.

[172] See Shawn Harmon, Graeme Laurie and Aidan Courtney, 'Dignity, Plurality and Patentability: The Unfinished Story of Brustle v Greenpeace (Case Comment)' (2013) 38(1) European Law Review 38(1) 92; Ana Nordberg and others, 'Cutting Edges and Weaving Threads in the Gene Editing (Я)evolution: Reconciling Scientific Progress with Legal, Ethical, and Social Concerns' (2018) 5(1) Journal of Law and the Biosciences 35.

multiple types of uses – including some ethically objectionable and some highly desirable – the problem remains on how to reduce incentives to the first and still incentivise the latter. Finally, the implementation of the European model as a type of public technology governance tool is highly dependable on the existence of a fully-functioning patent examination system and cannot be adopted in countries with a mere patent recognition system.

2.3.3. Research exemptions and compulsory licences

As mentioned above, the TRIPS Agreement also provides the basis for WTO members to introduce into national law and procedures post-grant limitations on the scope of protection of a patent through the existence of certain in-built flexibilities. These flexibilities include (i) research exemptions and (ii) compulsory licences.

2.3.3.1 Research exemptions

The exclusionary rights conferred by a patent should contribute to the promotion of technological innovation and to the transfer and dissemination of technology.[173] However, an absolute exercise of the exclusionary right in TRIPS Article 28, runs the risk of creating deadweight losses and limiting the spread of knowledge. TRIPS Article 30 provides a basis for members to fine tune the balance of interest between different stakeholders by introducing limitations to the rights conferred by a patent. Research exemptions[174] are one such limitation widely adopted in patent systems around the world. Allowing third parties to investigate an invention is considered a cornerstone of the patent system's quid pro quo of granting an exclusionary right under the premise that the invention is disclosed to the public. Research exemptions allow individuals to make use of that disclosure and enable, for example, follow on inventions. However, the introduction of limitations to the rights conferred by a patent create an important demarcation line between private and public governance of patented inventions, limiting the possibility of patentees to e.g. impose restriction on the use of a technology or compliance with ethical norms via licenses.

Article 30 of the TRIPS Agreement sets out three conditions, the so-called three-step-test,[175] to be met when applying such limitations in national laws: they must be *limited*, not unreasonably conflict with the *normal exploitation* of the patent and not unreasonably prejudice the *legitimate interests* of the patent owner, taking account of the legitimate interests of third parties. The criteria are cumulative and must be understood in relation to each other. Whether a limitation comply with the criteria set out in art 30 revolves firstly,

[173] Article 7, World Trade Organization, Agreement on Trade-Related Aspects of Intellectual Property Rights (as amended on 23 January 2017), Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, signed in Marrakesh, Morocco on 15 April 1994, <https://www.wto.org/english/docs_e/legal_e/31bis_trips_01_e.htm> accessed 27 July 2021.

[174] Terminology is not unanimous and reference is made to "experimental use exceptions", "Research exception" and "research Exemption". Here they are used interchangeably.

[175] Modelled on the three-step test in art. 9(2) of the Berne Convention for the Protection of Literary and Artistic Works <https://wipolex.wipo.int/en/text/283693> accessed 27 July 2021.

on an assessment of the extent to which the patent owner's rights have been curtailed[176]. Secondly, the effect of the limitation on the commercial activity necessary to exploit the patent should be evaluated.[177] And finally, the balancing of 'justifiable' interests, i.e. interests supported by relevant public policies or other social norms, should be assessed.[178]

Carving out safe-harbours for research-use of patented inventions has been deemed necessary in many jurisdictions. However, substantial national and regional differences in the adoption and scope of research exemptions to the patent protection subsist.[179] Distinctions between research *on* and *with* a patented invention and when research is considered *commercial* are two important features shaping the scope of the various national research exemptions. A national research exemption may for example allow for both research on and with a patented invention, but only let the exemption apply to non-commercial research, narrowing the scope of application. A robust exception for research has been adopted in most European countries, though still with some significant differences between countries regarding exception from research *on* or *with* the invention. Both research on and with are, for example, allowed in Belgium,[180] while only research *on* the patented invention is allowed in the Scandinavian countries and Germany.[181] The Adean Pact (Article 53) provides the legal basis for a research exception in e.g. Columbia, Ecuador, Peru and Venezuela, allowing experimentation on the subject matter and acts carried out exclusively for the purposes of teaching or scientific or academic research. In the US, there is no statutory research exception and an extremely narrow research exception developed in case law only allowing "philosophical enquiry"[182] even though there have been many calls to create a firm legal basis for a broader research exemption.

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[176] Canada – Patent Protection of Pharmaceutical Products, Report of the Panel, WT/DS114/R, 17 March 2000, paragraph 7.32-7.33.

[177] Canada – Patent Protection of Pharmaceutical Products, Report of the Panel, WT/DS114/R, 17 March 2000, paragraph 7.54-7.55.

[178] Canada – Patent Protection of Pharmaceutical Products, Report of the Panel, WT/DS114/R, 17 March 2000, paragraph 7.69 and 7.71.

[179] Jakob Wested and Timo Minssen 'An Update on Research-& Bolar Exemptions in the US and Europe: Unsolved Questions and New Developments in an Increasingly Important Area of Law' (2019) 2 NIR: Nordiskt Immateriellt Rättsskydd 168.

[180] This rather broad research exception is currently still applicable in Belgium. However, new legislation was adopted to align the provision in Belgian patent law with the relevant provision in the Unified Patent Court Agreement (an international treaty adopted in December 2012 as part of the 'Unitary Patent Package' which will significantly alter the patent system in Europe once it will enter into force, but which has been blocked for many years due to the Brexit and several other legal challenges). The new legislation will only enter into force, if and when the UPC Agreement will enter into force. See: ''Europe: seeking competitive research exemptions in view of the UPC Agreement - the Belgian example' <www.twobirds.com/en/news/articles/2018/belgium/europe-seeking-competitive-research-exemptions-in-view-of-the-upc-agreement-the-belgian-example> accessed 28 July 2021.

[181] András Kupecz and others, 'Safe Harbours in Europe: An Update on the Research and Bolar Exemptions to Patent Infringement' (2015) 33(7) Nature Biotechnology 710.

[182] *Whittemore v. Cutter* 29 Fed. Cas. 1120 (C.C.D. Mass. 1813); *Madey v. Duke University* 037 F.3d 1351 (Fed. Cir. 2002); *Bowman v. Monsanto Co.* 133 S.Ct. 1761 (2013).

Box 2. Countries with national laws providing research exemptions from patent infringement include:

Albania, Algeria, Andorra, Antigua and Barbuda, Argentina, Armenia, Australia, Azerbaijan, Barbados, Belarus, Belgium, Belize, Bhutan, Bolivia, Bosnia and Herzegovina, Botswana, Brazil, Bulgaria, Burkina Faso, Canada, China, Hong Kong(China), Colombia, Costa Rica, Croatia, Cyprus, Czech Republic, Democratic People's republic of Korea, Denmark, Dominica, Dominican Republic, Ecuador, Egypt, El Salvador, Estonia, Ethiopia, Finland, France, Germany, Ghana, Greece, Guatemala, Honduras, Hungary, Iceland, India, Indonesia, Ireland, Israel, Italy, Japan, Jordan, Kazakhstan, Kenya, Kyrgyzstan, Latvia, Lebanon, Liberia, Lithuania, Luxembourg, Malaysia, Malta, Mauritius, Mexico, Mongolia, Morocco, Mozambique, Namibia, Netherlands, New Zealand, Nicaragua, Norway, Oman, Pakistan, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Poland, Portugal, Republic of Korea, Republic of Moldova, Romania, Russian Federation, Saint Lucia, Sao Tome and Principe, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, Spain, Sri Lanka, Sweden, Switzerland, Tajikistan, Thailand, The Former Yugoslav Republic of Macedonia, Tonga, Trinidad and Tobago, Tunisia, Turkey, Uganda, Ukraine, United Kingdom, United States of America, United Republic of Tanzania, Uruguay, Uzbekistan, Vietnam and Zambia.

Source: WIPO Standing Committee of the Law of Patents (SCP), November 2018.[183]

Research exemptions in national laws and private governance mechanisms allowing research use can be complimentary as, for example in the US, where a very limited research exemption is complemented by a culture of self-imposed limitations to patent enforcement.[184] However, significant uncertainty regarding the adoption of such pledges and practices and their interpretation subsist.[185] Furthermore, in areas with a high density of patents[186] making it extremely difficult to identify relevant licensors or inducing exorbitant licensing costs due to royalty stacking, research exemptions have also been called for as part of the solution.[187] In that perspective research exemptions for patent protection in national laws have the potential to provide a useful mechanism to ensure

[183] WIPO, Standing Committee on the Law of Patents, Twenty-Ninth Session Geneva, December 3 to 6, 2018, Reference document on Research Exceptions, SCP/29/3, 26 November 2018 <www.wipo.int/edocs/mdocs/scp/en/scp_29/scp_29_3.pdf> accessed 27 July 2021.

[184] This has also been referred to as a practice of "rational forbearance", see Jakob Wested, 'Applying Patents & Imagining Openness: Patenting Enabling Technologies in Synthetic Biology, the Case of CRISPR' (PhD thesis, University of Copenhagen 2017) 243.

[185] See e.g. Jorge L Contreras, and Jacob Meredith (eds), *Patent Pledges: Global Perspectives on Patent Law's Private Ordering Frontier* (Edward Elgar 2017).

[186] Also referred to as "patent thickets" and "anti-commons", see e.g. Michael A Heller and Rebecca S Eisenberg, 'Can Patents Deter Innovation? The Anticommons in Biomedical Research' (1998) 280(5364) Science 698; Rebecca S Eisenberg, '*Anticommons, Transaction Costs, and Patent Aggregators* in Ben Depoorter, Peter Menell and David Schwartz (eds) *Research Handbook on the Economics of Intellectual Property Law* (Edward Elgar 2019) 27.

[187] Naomi Hawkins, 'The Impact of Human Gene Patents on Genetic Testing in the United Kingdom' (2011) 13(4) Genetics in Medicine 320.

transparent, inclusive and equitable access to explore new technologies such as CRISPR.

2.3.3.2 Compulsory licences

Consideration has also been given to the extent that compulsory licences can assist in ensuring access to new technologies such as CRISPR.[188] Under certain circumstances a compulsory or non-voluntary licence may be granted by a competent national authority to a third party, allowing the exploitation of the patented invention during the patent term without the authorisation of the right holder. In particular, a third party may be permitted to use, sell or import the patent-protected product or process without the patent owners' consent. This authorisation may also be granted to a government agency or a third party authorised to act on behalf of the government, in which case such authorisation is referred to as government use. Reasons for granting compulsory licences may include balancing the rights of patent holders with the public interest, achieving public health objectives, or addressing anti-competitive behaviour.[189]

Article 5A of the Paris Convention for the Protection of Industrial Property (1967) recognises the right of each country of the Paris Union to take legislative measures providing for the grant of compulsory licences to prevent abuses which might result from the exercise of excluding rights conferred by the patent, for example failure to work the invention. Paris Union member countries are free to define what constitutes "abuses which might result from the exercise of exclusive rights conferred by the patent" or "failure to work".[190]

The TRIPS Agreement, Article 2.1, provides that all WTO members shall comply with, *inter alia,* Article 5A of the Paris Convention concerning compulsory licences. In addition, under Article 31 of the TRIPS Agreement, a WTO member may allow, under stipulated conditions, other use than that allowed under Article 30 without authorisation of the right holder. Those uses include compulsory licences and government use. Article 31*bis* also allows a special compulsory licence permitting patented pharmaceutical products made under such licence to be exported to countries lacking national production capacity in the pharmaceutical sector.[191]

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[188] See, for example, Robin Feldman, 'The CRISPR Revolution: What Editing Human DNA Reveals About the Patent System's DNA' (2016) 64 UCLA Law Review Discourse 392.

[189] Secretariat for the Thirtieth Session of the WIPO Standing Committee on the Law of Patents (SCP) 24-27 June 2019, 'Draft Reference Document on the Exception Regarding Compulsory Licensing' SCP/30/3, 31 May 2019, <www.wipo.int/edocs/mdocs/scp/en/scp_30/scp_30_3-main1.pdf> accessed 29 July 2021, 4-6.

[190] World Intellectual Property Organization, *Paris Convention for the Protection of Industrial Property*, <https://wipolex.wipo.int/en/text/287556> accessed 29 July 2021.

[191] World Trade Organization, Agreement on Trade-Related Aspects of Intellectual Property Rights (as amended on 23 January 2017), Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, signed in Marrakesh, Morocco on 15 April 1994 <www.wto.org/english/docs_e/legal_e/31bis_trips_01_e.htm> accessed 29 July 2021.

Box 3. Countries with national laws providing for compulsory licensing include:

Albania, Algeria, Andorra, Antigua and Barbuda, Argentina, Armenia, Australia, Austria, Azerbaijan, Bahrain, Bangladesh, Barbados, Belarus, Belgium, Belize, Benin*, Bhutan, Plurinational State of Bolivia, Bosnia and Herzegovina, Botswana, Brazil, Brunei Darussalam, Bulgaria, Burkina Faso*, Burundi, Cabo Verde, Cambodia, Cameroon*, Canada, the Central African Republic*, Chad*, Chile, China, Hong Kong (China), Colombia, Comoros*, Congo,* Costa Rica, Côte d'Ivoire,* Croatia, Cuba, Cyprus, Czech Republic, Democratic People's Republic of Korea, Denmark, Djibouti, Dominica, Dominican Republic, Ecuador, Egypt, El Salvador, Equatorial Guinea*, Estonia, Eswatini, Ethiopia, Finland, France, Gabon*, Gambia, Georgia, Germany, Ghana, Greece, Grenada, Guatemala, Guinea*, Guinea-Bissau*, Honduras, Hungary, Iceland, India, Indonesia, Iran, Iraq, Ireland, Israel, Italy, Japan, Jordan, Kazakhstan, Kenya, Kyrgyz Republic, Lao People's Democratic Republic, Latvia, Lebanon, Libya, Liechtenstein, Lithuania, Luxembourg, Madagascar, Malaysia, Mali,* Malta, Mauritania,* Mauritius, Mexico, Monaco, Mongolia, Montenegro, Morocco, Mozambique, Namibia, Netherlands, New Zealand, Nicaragua, Niger,* Nigeria, North Macedonia, Norway, Oman, Pakistan, Papua New Guinea, Paraguay, Peru, Philippines, Poland, Portugal, Qatar, Republic of Korea, Republic of Moldova, Romania, Russian Federation, Saint Lucia, Sao Tome and Principe, Saudi Arabia, Senegal,* Serbia, Singapore, Slovak Republic, Slovenia, South Africa, Spain, Sri Lanka, Sudan, Sweden, Switzerland, Syrian Arab Republic, Tajikistan, Thailand, Togo*, Tonga, Trinidad and Tobago, Tunisia, Turkey, Turkmenistan, Uganda, Ukraine, United Arab Emirates, United Kingdom, United Republic of Tanzania, United States of America, Uruguay, Uzbekistan, Viet Nam, Zambia, and Zimbabwe

"*" The Bangui Agreement provisions on, *inter alia*, non-voluntary licenses are applicable in Member States of the African Intellectual Property Organization (OAPI).

Source: WIPO Standing Committee of the Law of Patents (SCP), May 2019.[192]

The Declaration on the TRIPS Agreement and Public Health, adopted by the Fourth Session of the WTO Ministerial Conference at Doha on 14 November 2001, also provides some guidance for the interpretation and application of Article 31.[193] The Declaration states, in paragraph 4, that WTO Members agree that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health.

[192] ibid.

[193] World Trade Organization, Doha Declaration on the TRIPS Agreement and Public Health, adopted 14 November 2001 <www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm> accessed 29 July 2021.

Accordingly, while reiterating the commitment to the TRIPS Agreement, the WTO members affirmed that the Agreement can and should be interpreted and implemented in a manner supportive of the WTO members' right to protect public health and, in particular, to promote access to medicines for all. In this connection, the Members reaffirmed the right of WTO members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose.[194]

As resource-constrained countries seek to ensure access to human genome inventions in the future, it can be anticipated that further attention will be paid to the extent that compulsory licensing can be used as a policy tool to balance the rights of patent holders with the public interest, to achieving public health objectives, or to address anti-competitive behaviour.

2.3.4. The precautionary principle

Another reminder of the highly contested landscape in this innovation is in growing calls from those seeking to oppose the grant of human genome editing patents, for greater consideration to be paid to the precautionary principle.[195] The essence of this is that if there is risk of severe adverse impact – often for the environment or public health – from a particular activity, then there should be an intervention to prevent that impact, even if there is no scientific evidence which can, at that time, confirm the risk. This (lack of) action should be the subject of a review as evidence changes – although it is argued that often this later review does not occur, and that the application of precaution can be more of a single decision.[196] The precautionary principle (or sometimes the looser "precautionary approach") can be found in international instruments such as the Rio Declaration on Environment and Development 1992,[197] the UN Framework Convention on Climate

[194] For further discussion see Duncan Matthews, 'WTO Decision on Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health: A Solution to the Access to Essential Medicines Problem?' (2004) 7 *Journal of International Economic Law* 73; Duncan Matthews, 'From the August 30, 2003 Decision WTO Decision to the December 6, 2005 Agreement on an Amendment to TRIPS: Improving Access to Medicines in Developing Countries?' (2006) 10 *Intellectual Property Quarterly* 91; Duncan Mattthews and Carlos Correa, United Nations Development Programme Discussion Paper, *The Doha Declaration Ten Years On and Its Impact on Access to Medicines and the Right to Health* (2011) <www1.undp.org/content/dam/undp/library/hivaids/Discussion_Paper_Doha_Declaration_Public_Health.pd> accessed 29 July 2021.

[195] See consideration by Justine Pila, 'Adapting the *Ordre Public* and Morality Exclusion of European Patent Law to Accommodate Emerging Technologies' (2020) 38 *Nature Biotechnology* 555; Estelle Derclaye, 'Should Patent Law Help Cool the Planet? An Enquiry from the Point of View of Environmental Law Part 2' (2009) 31 EIPR 227, 230.

[196] Cass Sunstein, 'Beyond the Precautionary Principle' (John M. Olin Program in Law and Economics Working Paper No. 149, 2002); Steve Clarke, 'Cognitive Bias and the Precautionary Principle: What's Wrong with the Core Argument in Sunstein's Law of Fear and How to Fix It' (2010) Journal of Risk Research 13(2) 163-174; Emmanuelle Tuerlings, 'Background Paper Governance 1. Human Genome Editing' (WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, 2019), 25-8; European Commission, 'Ethics of Genome Editing' (2021). EGE 2021 report, <https://ec.europa.eu/info/sites/default/files/research_and_innovation/ege/ege_ethics_of_genome_editing-opinion_publication.pdf> accessed 27 July 2021.

[197] A/CONF.151/26 (Vol. I), Principle 15.

Change 1992)[198] and Convention on Biological Diversity 1992 (CBD).[199] From the EU perspective, the Treaty on the Functioning of the European Union[200] provides that Union policy on the environment shall be based on the precautionary principle,[201] and contribute to preserving, protecting and improving the quality of the environment and to protecting human health,[202] and the Union shall take account of available scientific and technical data and to the potential benefits and costs of action or lack of action.[203]

The precautionary principle is not new to patents, and there are established arguments that it can enable states to take a more proactive approach to compulsory licensing of pharmaceutical patents, including through engagement with human rights and international health instruments.[204] There is ongoing debate as to whether the exclusions to patentability encompassed in the EU Biotechnology Directive[205] and, by association, the EPC Implementing Regulations[206] embody the precautionary principle as so enshrined in the TFEU and should (or could) be taken into account by patent granting authorities when determining whether a European patent should be issued.[207] There are also views that the precautionary principle should form part of interpretation of TRIPS given that many parties to TRIPS are also parties to the CBD.[208] Scholars concerned about patenting have also argued that technological uncertainty about the impact of HGE should not prevent intervention; in this context, intervention would mean patent offices being prepared to decline to grant a patent on the basis of the commercial exploitation, '*ordre public'* and morality provision.[209] As noted in 2.3.3, such an approach could be

[198] https://unfccc.int/resource/docs/convkp/conveng.pdf, art 3(3).
[199] https://www.cbd.int/doc/legal/cbd-en.pdf, preamble 9.
[200] Article 191 TFEU OJ C326/47 26 October 2012.
[201] Article 191(2).
[202] Article 191(1).
[203] Article 191(3). See also Commission of the European Communities, Communication from the Commission on the precautionary principle, COM(2000) 1 final <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2000:0001:FIN:EN:PDF> accessed 27 July 2021.
[204] See eg Phoebe Li and Pheh-Hoo Lim, 'A Precautionary Approach to Compulsory Licensing of Medicines: tempering Data Exclusivity as a Obstacle to Access' (2014) 3 IPQ 241; Phoebe Li, *Health Technologies and International Intellectual Property Law:A Precautionary Approach* (Routledge 2013).
[205] Articles 5 and 6.
[206] Rules 28 and 29.
[207] See, for instance, Graham Reynolds, 'The Precautionary Principle and its Application in the Intellectual Property Context: Towards a Public Domain Assessment' in B Courtney Doagoo and others (eds) *Intellectual Property for the 21st Century: Interdisciplinary Approaches* (Irwin Law 2013) 95; Ana Nordberg and others, 'Cutting Edges and Weaving Threads in the Gene Editing (*Я*)evolution: Reconciling Scientific Progress with Legal, Ethical and Social Concerns" (2018) 5(1) *Journal of Law and Biosciences* 35, 37 sum up (at 49-50) that CRISPR-Cas9 and the future of gene-editing technology can potentially produce enormous benefits to humans, but the uncertainty about possible harm that may result from large-scale gene editing means that a precautionary approach is advisable to policy decisions that respect a proportionality constraint on acceptable precautions.
[208] See Angelica Bonfanti, 'Environmental Risk in Biotech Patent Disputes' 2012 EJRR 2012, 3(1), 47-56,53-6 and see <www.wto.org/english/thewto_e/whatis_e/tif_e/org6_e.htm> and </www.cbd.int/information/parties.shtml>.
[209] See Justine Pila, 'Adapting the *Ordre Public* and Morality Exclusion of European Patent Law to Accommodate Emerging Technologies' (2020) 38 *Nature Biotechnology* 555, arguing for there to be a holistic risk assessment document of the innovation's "economic, cultural, ethical and political significance" to inform decisions of grant in a precautionary process, opening up the application of power by the patent offices, notably in the context of risk and transparency.

argued to have a negative impact on innovation incentives. Further, it would be an indirect governance step, as the lack of a patent does not mean that technology cannot be used.

Embracing the precautionary principle in this manner would be a jump by decision makers over previous practice. This would be particularly so for the EPO given that, as noted, its regulations do not involve it applying the EU treaties, and the EPO is not a member to the international environmental treaties discussed. Arguments for using precaution are stronger for individual member states who have their own similar provisions in their national laws[210] and are parties to the CBD; and the same is so for countries beyond Europe who are in a similar position; yet actually including precaution in patent grant would still be novel. It is noteworthy, however, that in other areas of law there are examples of decision makers being willing to act creatively and apply the precautionary principle in other areas of societal uncertainty. Consider the high profile decision in the Netherlands when the court considered that the precautionary approach should be taken in a decision involving climate change and rights to life and health in the European Convention on Human Rights[211] In Pakistan, the Supreme Court upheld a refusal to permit the construction of cement plants in a particular area, referring to the Rio Declaration and to the provincial government being obliged to take a precautionary approach.[212] The decisions in these cases are not of course directly relevant to the possible decisions of patent offices. The points made above, however, from scholars in relation to the use of the precautionary principle in relation to patents suggest that individuals and NGOs objecting to patents may use the greater embracing of precaution in other areas of law as a new base to advance their position. If a patent office chose to follow it, this could lead to them taking a restrictive approach to grant if the challenger puts forward evidence which indicates a risk to health and the environment of commercial exploitation of HGE. The possibility of this should be borne in mind - it is another part of the evolving and uncertain landscape which can be relevant to public governance.

2.4. Private Governance

As highlighted above, the exclusionary nature of patent rights allows right-holders to "govern" as private actors over a patented technology. Notably, patent rights are negative in nature. The grant of a patent does not mean one can use a patented technology in any possible ways – rather the use of a technology must still comply with other regulatory frameworks. Nonetheless, if there is no legal prohibition against the use of a patented technology, the patent allows rights holders to control how that technology can be used, and by whom, for the duration of the patent. Right- holders can give permission to third parties to use a patented technology by issuing a license. If third parties use patented technologies without a license from the rights holder they are liable to be challenged via

[210] See Box 1.
[211] *Netherlands v Urgenda Foundation* 19/00135, [5.3.2] [5.6.2].
[212] CP 1290 - L 2019 *DG Khan Cement Company v Government of Punjab* (2021) <http://climatecasechart.com/climate-change-litigation/wp-content/uploads/sites/16/non-us-case-documents/2021/20210415_13410_judgment.pdf> [16] [17].

patent infringement litigation which can be a strong deterrent to third parties against use of a patented technology without rights holders' permissions.

The type and nature of the licensing strategy adopted by rights holders is a key component to how patented technologies can be used. Three main types of licensing strategies can be adopted around *who can use* the inventions which are considered in this section, namely: exclusive, non-exclusive and collaborative licensing strategies. The particular type of license and detailed licensing conditions will also have a considerable impact on the price (royalties, license fee) required by the patent holder. Having considered this aspect, we then examine how patent licensing/enforcement strategies could be used to affect the *substantive terms for how a* patented technology is used, focusing on ethical licensing and defensive enforcement of patent rights.

2.4.1. Exclusive Licensing

An exclusive license is a license whereby the rights holders exclusively license the technology to another entity (the licensee); an exclusive license, hence, also prevents the rights holder from using the licensed technology for the described field of use or identified territories. The licensee obtains the right to exclusively use the technology under patent for the duration of the license. Exclusive licensing was a typical licensing strategy for earlier forms of genome editing.[213] This strategy means that only a few actors have control over a patented technology, and are expected to police it. In the biomedical sector it is not uncommon to adopt some kind of 'surrogate licensing strategies'.[214] Surrogate licensing is a type of licensing whereby the rights holder grants exclusive rights over their technologies to a spin-off company or a so-called 'surrogate' licensing company. Surrogate licensing companies can be granted an exclusive right to sub-license the patented technologies in such contexts. Such companies can then effectively control how such patent rights are licensed to third parties. In the CRISPR context, many patent holders gave surrogate licensing companies exclusive rights to use patented CRISPR technologies to develop any human therapeutics, targeting any gene on the human genome.[215] Surrogate licensing companies can also sub-license such rights to other entities who may be interested in developing therapeutics. Nonetheless, the use of exclusive rights in this way can be problematic, as Contreras and Sherkow highlight: "[g]iving one company an exclusive right to use CRISPR to develop human therapies targeting every segment of the human genome could thus limit the creation of potentially beneficial therapies." Such licensing strategies have the potential to rapidly "bottleneck the use of CRISPR technology to discover and develop useful human therapeutics."[216]

[213] Gregory D Graff and Jacob S Sherkow (2020), 'Models of Technology Transfer for Genome-Editing Technologies' (2020) 21(1) Annual Review of Genomics and Human Genetics 509.
[214] Gregory D Graff and Jacob S Sherkow (2020), 'Models of Technology Transfer for Genome-Editing Technologies' (2020) 21(1) Annual Review of Genomics and Human Genetics 509.
[215] Jorge L Contreras & Jacob S Sherkow, 'CRISPR, Surrogate Licensing, and Scientific Discovery' (2017) 355 Science 698, 699.
[216] Jorge L Contreras and Jacob S Sherkow, 'CRISPR, Surrogate Licensing, and Scientific Discovery' (2017) 355 Science 698, 699.

2.4.2. Non-exclusive Licensing

Alternatively, non-exclusive licensing can be used, whereby the license granted does not confer exclusive use on the licensee, and instead the rights holder can continue to exploit the technology, including by licensing others to use the technology for the same field of use and the same territories. Non-exclusive licenses can involve licensing fees/royalties but may also be free. This will be up to the rights holder to determine. As multiple entities can gain licenses under a non-exclusive licensing approach this can increase the competition amongst providers in a field. Non-exclusive licensing has been widely deployed in the biotechnology context, in particular for platform technologies that are widely used, such as PCR.[217]

2.4.3. Collaborative Licensing - Patent Pooling and Clearing Houses

In light of the fragmented patent landscape for CRISPR technologies (see Section 2.2.1.) and the potential bottlenecks which are occurring, proposals have been made to use collaborative licensing mechanisms in this context. Collaborative licensing mechanisms relate to licensing arrangements whereby multiple patent holders come together to license clustered patented technologies through one third party license for a reasonable royalty; such licensing arrangements act as a kind of “one-stop-shop”. Two main types of collaborative licensing strategies include patent pools or clearing houses.[218]

A patent pool arises, for example, in contexts where there are multiple patent rights regarding a specific technology, rights holders may choose to license such rights to each other. Following this, rights are bundled together into one package which can be licensed to third parties. This mechanism allows third parties to gain access to a package of relevant licenses in one step, rather than having to negotiate access for each patent right individually with each rights holder.[219] In the past, patent pools have, however, raised quite some concerns with competition authorities as they may act as a smokescreen for collusion and for the exchange of confidential business information. At the same time, the benefits in terms of transaction costs savings and prevention of royalty stacking tends to be recognized by competition authorities as well.

Clearinghouses are another type of collaborative licensing model, but slightly different from patent pools. They are sometimes compared to a supermarket model, where licensees shop around to collect access to the essential patented technology needed and the clearinghouse safeguards a reasonable royalty. Different from a pool, clearinghouses

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[217] Joe Fore Jr, Ilse R Wiechers and Robert Cook-Deegan, ‘The Effects of Business Practices, Licensing, and Intellectual Property on Development and Dissemination of the Polymerase Chain Reaction: Case Study’ (2006) 1 J Biomed Discovery & Collaboration 7 <https://j-biomed-discovery.biomedcentral.com/articles/10.1186/1747-5333-1-7> accessed 27 July 2021.

[218] Timo Minssen, Esther van Zimmeren and Jacob Wested, ‘Clearing a Way through the CRISPR Patent Jungle’ (2018) LSIPR, <www.lifesciencesipreview.com/article/clearing-a-way-through-the-crispr-patent-jungle> accessed 27 July 2021; Esther van Zimmeren and others, ‘Patent Pools and Clearinghouses in the Life Sciences’ (2011) 29(11) Trends in Biotechnology 569.

[219] See generally Esther van Zimmeren and others, ‘Patent Pools and Clearinghouses in the Life Sciences’ (2011) 29(11) Trends in Biotechnology 569.

are intermediaries that match patent rights holders and potential licensees. So, the collaboration between patent holders, which is required for the functioning of a pool and which may be considered risky from a competition perspective, is not required for clearinghouses.[220]

In theory, patent pools and clearinghouses can both be used to facilitate access to a large number of patents related to a particular technology, and in this way can be used as a means to deliver access to technology where multiple patent rights apply in a fragmented landscape like the genome editing context, avoiding so-called 'patent thickets'[221] (see Section 2.3.3.1.).[222] For instance, patent pools have been used heavily in the ICT and consumer electronics environment. They have proven to be particularly useful in parallel to efforts in standard setting in ICT and consumer electronics.[223] Where standards were being set, all users of the standardized technology would necessarily infringe on the patents on the underlying technology. For many years, owners of "essential patents" have been involved in setting up patent pools, licensing out their standardized, patented technologies under fair, reasonable and non-discriminatory (so-called FRAND) licensing conditions.[224] Today, many efforts are running regarding pools for Internet of Things technology, where the patent landscapes are highly fragmented as well. Nonetheless, the promises of high returns on investment and the heterogeneity of the interests of patent owners and licensees in the area of the Internet of Things creates many challenges in bringing the relevant patent owners to the table to establish an effective pool and to set reasonable licensing conditions.

For human genome editing, there has been discussion of the development of a CRISPR Pool coordinated by MPEG LA. In theory, such a joint licensing platform could be used to address some of the fragmentation aspects within the current patent landscape for CRISPR technologies. Such a "one-stop-shop" would be voluntary, market-based and would have a large number of potential users safeguarding the viability of the model and the generation of reasonable licensing revenue even when it needs to be shared with a large number of rights holders. After all, such a pool model would also result in significant transaction cost savings for the rights holders and could speed up market adoption. For licensees it would facilitate freedom to operate and would secure more transparency, predictability and reasonable royalty rates.

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[220] ibid.

[221] Carl Shapiro, 'Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard-Setting' in A Jaffe (ed) *Innovation Policy and the Economy* (The MIT Press 2001) 119; Esther van Zimmeren and others, 'Patent Pools and Clearinghouses in the Life Sciences' (2011) 29(11) Trends in Biotechnology 569.

[222] See footnote 185.

[223] Jorge L Contreras, 'Technical Standards, Standards-Setting Organizations and Intellectual Property: A Survey of the Literature (with an Emphasis on Empirical Approaches)' (2017) Utah Law Faculty Scholarship 11, <https://dc.law.utah.edu/cgi/viewcontent.cgi?article=1010&context=scholarship> accessed 27 July 2021.

[224] We note here that over the years, increasingly on a worldwide level disputes have arisen on the interpretation of what FRAND means and what obligations owners of standard essential patents have *vis-à-vis* willing potential licensees. However, a detailed discussion of this topic is outside the scope of this paper.

In July 2017, the Broad Institute announced it had joined, with relevant joint patent holders the Rockefeller Institute, Harvard University and Massachusetts Institute of Technology, discussions to create a CRISPR-Cas9 licensing pool co-ordinated by MPEG LA.[225] The Broad Institute claimed that the pool would "create a one-stop shop for commercial users to license CRISPR patents without needing to navigate a complex patent and licensing landscape".[226] However, this proposal has met with limited interest from other relevant rights holders, and it remains to be seen how this proposal may develop in the future. Of course many questions are still open, for instance how to attract a wide heterogeneity of rights holders and licensees to the pool? Which patents should be in the pool? As no technical standard has yet emerged in this field, other criteria will need to be used to determine the "essential" nature of the patents in the pool. Moreover, what will be the licensing conditions?

Moreover, aside from issues around the need for more rights holders to participate in this proposed pool, the set-up of the pool and the licensing conditions, there are also questions around the feasibility of setting up such a patent pool for CRISPR. More specifically, it is not clear to what extent existing exclusive licenses granted in relation to CRISPR patents may affect the ability to set up such a pool. Given the costs related to the biotechnology/biopharma sectors in terms of the development of new products and costs from a regulatory approval perspective, there is often a preference for exclusive licensing to recoup costs, and this may likely affect the potential interest in and success of a proposed pooling model for CRISPR.[227] Finally, for now some of the key patent owners (Broad/MIT v. Berkeley) are involved in fierce patent oppositions and litigation regarding the granted patents (see Section 2.2.2). Until this has been sorted out, many less prominent patent owners will probably take a wait-and-see approach and will unlikely be eager to join the licensing platform.

Interestingly, MPEG LA has already expressed an interest in including certain exclusions in the pool licensing conditions e.g. regarding human genome editing. In theory, such provisions could play an important, complementary role in governing the use of human genome editing. We link this topic to the emergence of so-called "ethical licensing" covered in section 2.4.4.

Relatedly, licensing conditions could be imposed to encourage broader access to technologies under patent such as clauses whereby rights holders offer preferential terms for access to patented technologies for particular groups e.g., public hospitals,

[225] 'Broad Institute of MIT and Harvard joins discussions to create worldwide CRISPR-Cas9 licensing pool' (Broad Institute Press Releases, 10 July 2017) <https://www.broadinstitute.org/news/broad-institute-mit-and-harvard-joins-discussions-create-worldwide-crispr-cas9-licensing-pool> accessed 27 July 2021.
[226] 'Broad Institute of MIT and Harvard Joins Discussions to Create Worldwide CRISPR-Cas patent Pool' (*CISION PR Newswire,* 10 July 2017) <www.prnewswire.com/news-releases/broad-institute-of-mit-and-harvard-joins-discussions-to-create-worldwide-crispr-cas9-licensing-pool-300484973.html> accessed 27 July 2021.
[227] Jorge L Contreras and Jacob S Sherkow, "Patent Pools for CRISPR Technology—Response' (24 March 2017) 355(6331) Science 1274.

researchers, universities etc.[228] Such clauses can be adopted via collaborative licensing models including patent pools.[229] Moreover, research funders can impose clauses within funding agreements to encourage or mandate conditions on the accessibility of technologies developed using such funding and/or the sharing of intellectual property rights in certain contexts[230] – the need and potential for the use of such clauses particularly in the context of publicly funded health research is frequently discussed.[231]

2.4.4. Ethical Licensing Conditions

Patent licensing conditions can potentially be used to dictate or restrict how technologies under patent are used for the duration of the patent (generally 20 years as noted above). These so-called "ethical licensing conditions" are conditions included in patent licenses which seek to restrict specific uses of that patented technology by third party licensees. The aim of such clauses, where adopted to date, has been to "curtail or restrict uses of a technology to encourage more "ethical" uses of a technology as defined by the patent holder."[232] Used in this way, patent licenses have the potential to be used to guide or encourage 'ethical uses' of technologies subject to patent[233] – i.e. by including clauses in

[228] See discussion and examples in: Sarah Ali-Khan and Richard E Gold, 'Contracting to Counter Gene Patents — a 21st Century Solution to Access and Innovation' (*Harvard Law School/Petrie Flom Blog*, 22 May 2017 <https://blog.petrieflom.law.harvard.edu/2017/05/22/contracting-to-counter-gene-patents-a-21st-century-solution-to-access-and-innovation/> accessed 27 July 2021; Aisling McMahon, (2019) 'Gene Patents and the Marginalisation of Ethical Issues' (2019) 41(10) European Intellectual Property Review 608; Aisling McMahon, 'Accounting for Ethical Considerations in the Licensing of Patented Biotechnologies and Health-Related Technologies: A Justification' in Naomi Hawkins (eds) *Patenting Biotechnological Innovation: Eligibility, Ethics and Public Interest* (Edward Elgar 2022). See also, more generally' Netherlands Federation of University Medical Centers, 'Ten principles for Socially Responsible Licensing' (June 2019) <www.nfu.nl/sites/default/files/2020-08/19.4511_Ten_principles_for_Socially_Responsible_Licensing_v19-12-2019.pdf> accessed 27 July 2021; Jenilee M Guebert and Tania Bubela, 'Implementing Socially Responsible Licensing for Global Health: Beyond Neglected Diseases' (2014) 6 Science Translational Medicine 260.

[229] Geertrui van Overwalle (ed), *Gene Patents and Collaborative Licensing Models: Patent Pools, Clearinghouses, Open Source Models, and Liability Regimes* (Cambridge University Press, 2009) v.

[230] Ana Nordberg ''Big Science, Big Data, Big Innovation? ERIC Policies on IP, Data and Technology Transfer' in Ulf Maunsbach and Olof Hallonsten (eds) Big Science and the Law (ExTuto publishing, forthcoming Sep. 2021).

[231] For example, in the COVID-19 vaccine context, Human Rights Watch recommended all governments attach conditions to the funding of COVID-19 vaccine research. See Human Rights Watch, ''Whoever Finds the Vaccine Must Share It' Strengthening Human Rights and Transparency Around Covid-19 Vaccines' (October 2020) <www.hrw.org/sites/default/files/media_2020/10/globalvaccine1020_web.pdf> accessed 27 July 2021.

[232] Aisling McMahon, 'Biotechnology & Patents as Private Governance: The Good, the Bad, the Potential for Ugly?' (2020) 3 Intellectual Property Quarterly 161, 166. See also the discussion in Jacob S Sherkow, 'Patent Protection for CRISPR: An ELSI Review' (2017) 4(3) Journal of Law and the Biosciences 565; Christi J Guerrini and others, 'The Rise of the Ethical License' (2017) 35 Nature Biotechnology 22; Oliver Feeney and others, 'Patenting Foundational Technologies: Lessons From CRISPR and Other Core Biotechnologies' (2018) 18(2) The American Journal of Bioethics 36.

[233] ibid. Aisling McMahon, 'Biotechnology & Patents as Private Governance: The Good, the Bad, the Potential for Ugly?' (2020) 3 Intellectual Property Quarterly 161.

the patent license which aim to prohibit or restrict ethically contentious uses of the technology under patent.

However, the meaning of 'ethical' in this context can differ depending on what the entity defining the licensing condition takes an 'ethical' use of a technology to be. Notably, the use of 'ethical licensing conditions' to direct ethical uses of a technology under patent appears to be still relatively rare practice. Examples of proposals for using patent licensing as a way to restrict uses of a patented technology, are given by the WHO's Expert Advisory Committee in its Report on "Human Genome Editing A Framework for Governance".[234] These include, in the 1990s discussions by the Wisconsin Alumni Research Foundation (the rights holder) which held consultations on whether it should include licensing restrictions on its patented stem cell lines to prohibit uses of these for reproductive cloning or development of non-human animal chimeras.[235]

More recently, the Broad Institute imposed three conditions in its licenses for uses of patents related to CRISPR-Cas9 gene editing techniques in the agricultural context. The conditions included a prohibition of uses of the licensed technology for gene drives, a prohibition on use of their licensed technology to create terminator or sterile seeds, and a prohibition of uses of their licensed technology to modify tobacco for commercial purposes.[236] These conditions were imposed by the Broad Institute due to concerns about how the technology under patent could be used downstream.[237] Moreover, others have discussed the potential for imposing ethical licensing conditions prohibiting the uses of patented gene editing technologies for gene drives.[238] Licensing clauses could also

[234] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: A Framework for Governance* (2021) <www.who.int/publications/i/item/9789240030060> accessed 27 July 2021, para 81-83.

[235] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: A Framework for Governance* (2021) <www.who.int/publications/i/item/9789240030060> accessed 27 July 2021, para 82.

[236] See Issi Rozen, "Licensing CRISPR for Agriculture: Policy Considerations' (*Broad Institute,* 29 September 2016) <https://www.broadinstitute.org/news/licensing-crispr-agriculture-policy-considerations> accessed 27 July 2021. See discussion in Jacob S Sherkow, 'Patent Protection for CRISPR: An ELSI Review' (2017) 4(3) Journal of Law and the Biosciences 565, 572; Aisling McMahon, 'Biotechnology & Patents as Private Governance: The Good, the Bad, the Potential for Ugly?' (2020) 3 Intellectual Property Quarterly 161,166.

[237] The Broad Institute stated in this context: "under the oversight of federal agencies in the United States, including the USDA, FDA, and EPA. Still, the Broad feels it is important to include explicit restrictions in the technology licenses as well. We wanted to share our thinking with others who may be considering licensing of related technologies". See Issi Rozen, "Licensing CRISPR for Agriculture: Policy Considerations' (*Broad Institute,* 29 September 2016) <https://www.broadinstitute.org/news/licensing-crispr-agriculture-policy-considerations> accessed 27 July 2021.

[238] Kevin M Esvelt 'Rules for Sculpting Ecosystems: Gene Drives and Responsive Science' in Irus Braverman (ed) *Gene Editing, Law and the Environment: Life Beyond the Human* (Routledge 2018) 21. See also Kevin M Esvelt 'Gene Drive Should Be a Non-Profit Technology' (*Stat News*, 27 November 2018) <www.statnews.com/2018/11/27/gene-drive-should-be-nonprofit-technology/> accessed 27 July 2021.

plausibly be used to aim to restrict contentious uses of patented human genome editing technologies.

However, whilst rights holder led ethical licensing approaches, may be laudable in terms of their aims, controversies arise around the role of ethical licensing conditions.[239] These include issues around the limitations of such approaches including, questions around whether rights holders, particularly if they are for-profit entities, would be likely to impose such conditions on uses of a technology – given that curtailing uses of a technology within a patent license, may make a license over that technology less attractive to third parties. Thus, it would not necessarily be in the financial interests of the rights holder.[240] Furthermore, from an accountability perspective, it is questionable if rights holders are the appropriate entity to design such conditions restricting how a technology under patent should be used for the duration of the patent. This is because such conditions can affect how a technology is used and can have knock-on implications for an entire field, particularly, if that patented technology is a platform type technology which other inventions rely upon for their operation.[241] Relatedly, questions around the decision-making process for how such clauses are designed arise. These questions include procedural justice issues, including the potential lack of democratisation within such approaches given the (potential for) limited recourse for the broader public or other stakeholders to input into the design of such clauses.[242] This issue of democratic deficits in the context of ethical licensing approaches to date is also recognised as problematic by the WHO's Advisory Committee's Report which states that "it is certainly not democratic, as the choice of whether to include restrictions is not made by the body politic" [243] (see Section 1.2.).[244]

Nonetheless, it is plausible that ethical licensing practices or guidelines, rather than be developed by rights holders, could instead be recommended by third parties such as international organisations e.g. the WHO, and recommended for adoption by rights

[239] For a more detailed discussion of the role of ethical licensing conditions and the development/regulation of technologies, see Aisling McMahon, 'Biotechnology, Patents and Licensing for 'Ethical Use': A Regulatory Opportunity?' (2021), Working paper, on file with the author; Aisling McMahon, 'Accounting for Ethical Considerations in the Licensing of Patented Biotechnologies and Health-Related Technologies: A Justification' in Naomi Hawkins (ed) *Patenting Biotechnological Innovation: Eligibility, Ethics and Public Interest* (forthcoming, Edward Elgar, 2022).

[240] Aisling McMahon, 'Biotechnology & Patents as Private Governance: The Good, the Bad, the Potential for Ugly?' (2020) 3 Intellectual Property Quarterly 161. In this context, – the Broad institute is a non-profit institute with a public health mandate – and thus, is likely a peculiar entity in comparison to other rights holders in this field, who may not have a public interest health mandate, and may be less likely to impose such conditions on use.

[241] ibid.

[242] Nienke de Graeff and others, 'Fair Governance of Biotechnology: Patents, Private Governance, and Procedural Justice' (2018) 18(12) The American Journal of Bioethics 57.

[243] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, *Human Genome Editing: A Framework for Governance* (2021) <www.who.int/publications/i/item/9789240030060> accessed 27 July 2021, para 84.

[244] See, in particular, the arguments set forth by the literature in footnotes 38 and 39.

holders or patent pools.[245] Such an approach could be used to bring together broader interdisciplinary expertise to develop clauses at an international level.

In such contexts, it must be borne in mind that patents relate to specific jurisdictions, as previously discussed. This means that what types of human genome editing technologies are patentable in different jurisdictions may differ due to differences in patentability criteria or exclusions that may be applicable. Rights holders that hold patents over such technologies may also differ across jurisdictions. This characteristic of patents is important when we consider the potential and also the limitations of ethical licensing clauses.[246] For example, it is entirely plausible that a technology will be patentable in one jurisdiction (region A) and not in another (region B), and that being the case, ethical licensing clauses will only operate in region A (where they are applicable). Nonetheless, ethical licensing clauses have many potential benefits which could be used to *complement* a broader governance approach to human genome editing. Moreover, adopting such clauses as part of a patent pool could also be beneficial, as it would likely encompass a greater number of rights holders who hold patents related to the technology in the genome editing context where multiple rights holders operate in the field, such as under the proposed MPEG LA CRISPR-Cas9 pool (2.4.3).

3. Conclusions

In this White Paper we have focused on the recommendations that relate specifically to patents and licensing issued in the WHO Expert Advisory Committee reports *Human Genome Editing: A Framework for Governance and Recommendations,* namely:

1. In collaboration with other international organizations, such as the World Intellectual Property Organization and the World Trade Organization and its Agreement on Trade-Related Aspects of Intellectual Property (the TRIPS Agreement), WHO should encourage relevant patent holders to help ensure equitable access to human genome editing interventions. This may include licensing costs proportional to the economic situation of a country.

2. WHO should encourage industry to work with resource-constrained countries to build capacity to take advantage of human genome inventions.

3. WHO should convene a meeting of those holding or applying for patents relevant to human genome editing, industry bodies, international organizations such as the World

[245] For a detailed discussion of such an approach, see Aisling McMahon, 'Biotechnology, Patents and Licensing for 'Ethical Use': A Regulatory Opportunity?' (2021), Working paper, on file with the author, which proposes a model for how this could operate. See also Aisling McMahon, 'Accounting for Ethical Considerations in the Licensing of Patented Biotechnologies and Health-Related Technologies: A Justification' in Naomi Hawkins (ed) *Patenting Biotechnological Innovation: Eligibility, Ethics and Public Interest* (forthcoming, Edward Elgar 2022).
[246] ibid.

Intellectual Property Organization and the World Trade Organization, and those involved in establishing or running relevant patent pools to explore the potential for the adoption of appropriate ethical licensing requirements.

In the light of the Expert Advisory Committee's *Recommendations*, in this White Paper we have elaborated on the potential role that patent grant procedures and licensing can play in the governance of human genome editing. We have sought to fill a gap in the wider policy debate, alongside the WHO Expert Advisory Committee reports, by setting out how the use of these technologies have already been shaped and regulated by private actors alongside regional or national patent law and examination practices, taking into account the flexibilities available under international patent treaties.

As such, we have combined an analysis of the potential of *private governance* through patenting and licensing strategies and *public governance* in shaping national and regional patent law in contributing to regulating human genome editing.

We summarise our main conclusions in response to the WHO Expert Advisory Committee's reports as follows:

3.1. The Expert Advisory Committee has made helpful recommendations for the next steps when considering the role that patents and licensing can play in the governance of human genome editing.

3.2. Patents and licensing, including ethical and compulsory licensing, play a significant role in the governance of human genome editing technologies as part of a toolkit consistent with the wider regulatory framework. Patent licensing and enforcement practices can be used, and are already being used, as instruments of governance to bring about socially responsible use as well as to deliver restrictive private control.

3.3. Patent licensing and enforcement practices involve the transfer of regulatory power from public to private actors and entail transaction costs, licensing fees, litigation costs, and can lead to uncertainty for third parties. This raises issues of transparency and accountability, and some anti-democratic concerns about how patent licensing and enforcement practices are being exercised in private hands.

3.4. Governments can set limits on the patentability of human genome editing as an instrument of governance, including the exclusion of certain inventions from patentability on grounds that the commercialization is contrary to '*ordre public'* and morality. Some governments have done so and there is variety in the application of patent law by courts and patent offices. Research exemptions and compulsory licences can also be used as tools of governance under national law and procedure in order to balance the rights of patent holders with the public interest, to achieve public health objectives, or to address anti-competitive behaviour.

3.5. Excluding technologies from patentability or curtailing those patent rights once granted has both the potential to diminish innovation incentives and increase access. It may have unwanted effects in the development of new health technology, may lead to a geographic displacement of research and technology development and impact on access to technology in ways that may have positive or negative effects on public health and the environment. Further discussions on international harmonisation should be encouraged and clarification of patent office practices and interpretative criteria concerning genome editing technologies would be welcome and desirable.

4. Recommendations

4.1. There is a need for greater understanding and more inclusive public debate on the role of patents and licensing in this area. The Expert Advisory Committee's *A Framework for Governance* and *Recommendations* implementation will undoubtedly help to stimulate this debate.

4.2. The need for public debate is particularly important for countries considering introducing or developing further guidance on the use of '*ordre public*' and morality exceptions to patentability in the area of genome editing or considering promoting post-grant patent governance through the use of research exemptions or compulsory licences.

4.3. The assessment of the risks and benefits of patent exclusions, exceptions and limitations need to be research-based taking into account inputs from all relevant stakeholders as well as those engaged directly in patent and innovation law and policy.

4.4. The role of private companies, research funding agencies, research institutions, academic and scientific self-governing bodies, and other stakeholders in promoting and developing private governance tools and best practices in patent licensing should be considered further. Patent pools offer one such option but, in the past, have proved difficult to operate in the biomedical sector. The challenges related to patent pools require special consideration in the context of human genome editing.

4.5. Alongside the Expert Advisory Committee's recommendation that the WHO should convene a meeting to explore the potential for the adoption of appropriate ethical licensing requirements, a landscaping study should be conducted as part of the proposed collaboration between the WHO, WIPO and WTO to identify which countries currently have '*ordre public'* and morality exceptions, how the law is then applied in practice when it is subject to decisions by patent offices and the courts and current public and private licensing practices.