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Original Article

Framing and legitimating EU legal regulation of human gene-editing technologies: key facets and functions of an imaginary

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ABSTRACT

Gene-editing technologies, ie those able to make changes in the DNA of an organism, are the object of global competition and a regulatory race between countries and regions. There is an attempt to craft legal frameworks protective enough for users, but flexible enough for developers of gene-editing technologies. This article examines the imaginary built into the framing of EU-level legal regulation of human gene-editing technologies and identifies its three key related facets: the tension around naturalness; safeguarding morality and ethics; and the pursuit of medical objectives for the protection of human health. Concerns around the use of gene-editing technologies in relation to eugenics and human enhancement have produced a multifaceted imaginary. We argue that this imaginary not only places a limit on EU-level regulation, despite a strong EU competence in respect of the internal market, but also seeks to ensure its legitimation.

KEYWORDS: European Union, framing, gene editing, imaginaries, law, science and technology studies

I. INTRODUCTION

A global uproar followed the 2018 announcement of Chinese scientist He Jian-Kui[1] that he had successfully used CRISPR[2] to edit the genes of twin embryos. The resulting twins, named Lulu and Nana, were born healthy, and with allegedly altered CCR5 genes, giving them resistance to the human immunodeficiency virus (or HIV). One of the greatest concerns culminating from the announcement is the use of gene-editing[3] technologies to modify the human germline. This had been subject to an international moratorium from scientists at the initiative of the United States of America, United Kingdom, and China, in 2015.[4]

The creation of the World Health Organization Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing in 2018[5] further demonstrates that the concerns around gene editing are now being progressively addressed at the global level. The European Union (EU) level of governance[6] tends to be missed from discussion of gene-editing technologies within legal scholarship.[7] Indeed, much attention remains on the national level, often in a

1 Henry T. Greely, *CRISPR'd Babies: Human Germline Genome Editing in the 'He Jiankui Affair'*, 6 J. Law Biosci. 111 (2019).

2 CRISPR is the abbreviation for 'Clustered Regularly Interspaced Palindromic Repeats' and CRISPR-Cas9 was hailed as the genome editing technology that would change the face of humankind. The CRISPR system could be programmed to target specific stretches of genetic code and to edit DNA at precise locations and, therefore, could potentially eradicate more genetic mutations and diseases in the future. See: Patrick D. Hsu, Eric S. Lander and Feng Zhang, *Development and Applications of CRISPR-Cas9 for Genome Engineering*, 157 Cell 1262 (2014).

3 The term 'gene editing' in this paper may be used interchangeably with the term 'genome editing', where appropriate, particularly in reference to external sources that may use the latter term. We use the term 'gene editing' as a targeted address to specific fragments in DNA that contain elements of heredity and the transmission of heredity processes. The term 'genome editing' has generally been used to broadly refer to the entire collection of DNA in an organism.

4 The 2015 summit led to a statement that opposed clinical use of modifications to the germline affecting the potential offspring, through changes to genes in gametes (sperm and eggs) and embryos, but approved the clinical use of somatic (body) cell gene therapies, which affect only the individual treated [Organizing Committee for the International Summit on Human Gene Editing, *On Human Gene Editing: International Summit Statement* (2015), https://www.nationalacademies.org/news/2015/12/on-human-gene-editing-international-summit-statement (accessed Sept. 24, 2020)]. Nevertheless, and despite the uproar over Jian-Kui's work, the Second International Summit was much more nuanced as it suggested that there should be a continuation of research and development of gene-editing technologies to treat diseases, possibly also where there is modification of the human germline, but its clinical use should be banned until safeguards conditions are met (Organizing Committee for the Second International Summit on Human Genome Editing, *Continuing the Global Discussion Proceedings of a Workshop—in Brief* (2019), https://www.nap.edu/read/25343/chapter/1 (accessed Sept. 24, 2020).

5 Dr Emmanuelle Tuerlings, *WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing* 37. For further discussion, see: European Group on Ethics in Science and New Technologies, *EGE Statement on Gene Editing* (2016), https://ec.europa.eu/info/sites/info/files/research_and_innovation/ege/gene_editing_ege_statement.pdf (accessed Jan. 2, 2020).

6 The EU's regulatory order is one level of the multilevel system of governance. Within that system the EU level interacts with a range of other regulatory orders including those at the national level. See further: Liesbet Hooghe and Gary Marks, Multilevel Governance and European Integration (2001).

7 For rare exceptions see: Jessica Almqvist and Cesare P. R. Romano, *The Regulation of Human Germline Genome Modification in Europe*, in Human Genome Germline Modification and the Right to Science: A Comparative Study of National Laws and Policies 155 (Andrea Boggio et al. eds.,

comparative approach,[8] or on the international level,[9] including linking human rights law and biotechnologies.[10]

Nevertheless, EU institutions are in the process of examining and assessing the issues raised by human gene editing. The European Medicines Agency (EMA)[11] and the European Commission, in collaboration with the European Group on Ethics in Science and Technologies (EGE),[12] have organized events, while the European Parliament has published a note on this topic.[13] The Council of the European Union has considered gene editing in relation to plants.[14] The EGE, from which an opinion on gene editing is awaited, proclaimed in a 2016 statement the need for inclusive debate that takes into account, among others, ethical principles such as human dignity, justice, equity, proportionality, and autonomy. Through this instrument of 'soft' law, ie an instrument that is non-binding but still has normative effects, the EGE emphasizes that 'ethical consideration needs to be given to all applications of gene editing, including the non-human applications'.[15]

A developing literature already focuses on the EU-level to highlight a range of legal regulation, including soft law, relating to gene-editing technologies.[16] This literature explains how EU law applies throughout the development pipeline for these technologies and health technologies more generally. The pipeline begins with an idea and, if

2020); Ana Nordberg et al., *Regulating Germline Editing in Assisted Reproductive Technology: An EU Cross-Disciplinary Perspective*, 34 Bioethics 16 (2020).

8 See for instance: Motoko Araki and Tetsuya Ishii, *International Regulatory Landscape and Integration of Corrective Genome Editing into In Vitro Fertilization*, 12 Reprod. Biol. Endocrinol. 108 (2014).

9 Achim Rosemann et al., *Heritable Genome Editing in a Global Context: National and International Policy Challenges*, 49 Hastings Cent. Rep. 30 (2019).

10 Biotechnologies and International Human Rights (Francesco Francioni ed., 2007); New Technologies and Human Rights (Therese Murphy ed., 2009).

11 EMA, *Report of the EMA Expert Meeting on Genome Editing Technologies Used in Medicinal Product Development* (2018), EMA/47066/2018.

12 European Commission and European Group on Ethics, *Open Round Table on the Ethics of Gene Editing* (2019), https://ec.europa.eu/info/events/round-table-ethics-gene-editing-2019-oct-16_en (accessed June 22, 2020).

13 European Parliament, *What If Gene Editing Became Routine Practice?* (2018), https://www.europarl.europa.eu/RegData/etudes/ATAG/2018/624260/EPRS_ATA(2018)624260_EN.pdf (accessed June 22, 2020).

14 Decision (EU) 2019/1904 Requesting the Commission to Submit a Study in Light of the Court of Justice's Judgment in Case C-528/16 Confédération paysanne *infra* note 51. Regarding the Status of Novel Genomic Techniques Under Union Law, and a Proposal, If Appropriate in View of the Outcomes of the Study, OJ 2019 L 293/103.

15 European Group on Ethics in Science and New Technologies, *EGE Statement on Gene Editing* (2016), https://ec.europa.eu/info/sites/info/files/research_and_innovation/ege/gene_editing_ege_statement.pdf (accessed Jan. 2, 2020). On 'soft' law, see: Gary E. Marchant and Brad Allenby, *Soft law: New Tools for Governing Emerging Technologies*, 73(2) Bull. Atomic Sci. 108 (2017). On the EGE and its 'soft' law, see: Helen Busby et al., *Ethical EU Law? The Influence of the European Group on Ethics in Science and New Technologies*, 33 Eur. L. Rev. 803 (2008).

16 Black defines regulation as 'the intentional use of authority to affect behaviour of a different party *according to set standards*, involving instruments of information-gathering and behaviour modification'—see: Julia Black, *Critical Reflections on Regulation*, 27 Aust. J. Leg. Philos. 1 (2002), emphasis added. This understanding of regulation includes 'hard law', 'soft law', social norms, standards and the market. See further: Robert Baldwin, Martin Cave and Martin Lodge, *Regulation—the Field and the Developing Agenda*, in The Oxford Handbook of Regulation (Robert Baldwin et al. eds., 2010); Robert Baldwin, Martin Cave and Martin Lodge, Understanding Regulation: Theory, Strategy, and Practice (2011).

development is successful, eventually results in a technology for market availability.[17] In this article, we focus on the main examples of EU-level 'hard' legal regulation, or fomally binding law, applicable to gene-editing technologies for humans throughout this pipeline.[18] We examine the imaginary of the future, or 'imagined future',[19] built into the framing of these main examples of EU-level 'hard' legal regulation. In doing so, we bring the latter literature from legal studies into dialogue with the developing discussion on imaginaries in science and technology studies (STS) and cognate disciplines. Our aim is to advance both the literature from legal studies, and the dialogue between it and STS,[20] and in turn to contribute toward awareness of the role of legal regulation in shaping the imagined future forming at the EU level of governance.

We argue that the facets or elements of a multifaceted imaginary—the tension around naturalness; safeguarding morality and ethics; and pursuing medical objectives for the protection of human health—are found in the framing of EU-level legal regulation. Framing involves discursive devices that organize experience, knowledge, and regulation.[21] The facets found in this framing are distributed between various legal instruments, which when looked at together, form a multifaceted imaginary. All together these facets conjure a future in which technoscience within the EU is steered toward innovations that exploit somatic gene editing for new medicinal products, but avoid editing of the human germ line.

The tension around naturalness is found in the eligibility for patents and the approach to genetically modified organisms (GMOs). Safeguarding morality and ethics is apparent in the exclusion from patentability of biotechnological inventions where their commercial exploitation would be contrary to *ordre public* or morality; the ethical review and prohibitions of research activities to be funded in the EU; and the prohibition of clinical trials that modify the germ line. The facet of pursuing medical objectives for the protection of human health is seen in maintenance of the exclusion from patentability of methods of therapeutic, diagnostic, and surgical treatment; and the incentives for the marketing of products based on gene-editing technologies as advanced therapy medicinal products (ATMPs).

The legislation discussed in this article is adopted predominantly under Article 114 of the Treaty on the Functioning of the European Union (TFEU).[22] This is the

17 Mark L. Flear, *Regulating New Technologies: EU Internal Market Law, Risk, and Socio-Technical Order*, in New Technologies and EU Law 74 (Marise Cremona ed., 2017). See the other contributions to the latter collection and also: European Law and New Health Technologies (Mark L. Flear et al. eds., 2013).

18 We do not, therefore, consider gene-editing technologies relating to plants or animals except where they relate to our focus on gene-editing technologies for humans.

19 The actual definition refers to 'imagined *futures*'—see: Jens Beckert, Imagined Futures: Fictional Expectations and Capitalist Dynamics (2016).

20 Dreamscapes of Modernity: Sociotechnical Imaginaries and the Fabrication of Power (Sheila Jasanoff and Sang-Hyun Kim eds., 2015). See also: Beckert, *Id.*; The Handbook of Science and Technology Studies (Ulrike Felt et al. eds., 2017).

21 Robert D. Benford and David A. Snow, *Framing Processes and Social Movements: An Overview and Assessment*, 26 Annu. Rev. Sociol. 611 (2000); Erving Goffman, Frame Analysis: An Essay on the Organization of Experience (1986); Maarten Hajer and David Laws, *Ordering through Discourse*, in The Oxford Handbook of Public Policy (Robert E. Goodin et al. eds., 2008); Vivien A. Schmidt, *Discursive Institutionalism: The Explanatory Power of Ideas and Discourse*, 11 Annu. Rev. Polit. Sci. 303 (2008).

22 Prior to the Treaty of Lisbon, which came into force on Dec. 1, 2009, Article 114 TFEU was Article 95 European Community Treaty, while Article 168 TFEU was Article 152 European Community Treaty.

main legal base for legislation relating to the establishment and functioning of the internal market.[23] The EU's legal competence in the public health field, Article 168 TFEU, which is an area of supporting, coordinating, or supplementary competence,[24] provides far more limited scope for legislation on gene-editing technologies. The so-called REACH legislation,[25] which is applicable to some new technologies, is not discussed because it is not applicable to human gene-editing technologies as long as they are medicinal products.[26] Other areas of law that are only very indirectly related to the regulation of gene-editing technologies, such as competition law, are also not discussed.[27] 'Soft' law at the EU level in the area under discussion has not yet fully emerged. Even if there were 'soft' law published to discuss, a comprehensive survey of it alongside 'hard' law would not be possible within a single article. As such, in what follows, we do not discuss 'soft' law.

This article does not examine interactions between national and EU levels of governance, including the imaginaries found at each level.[28] Such analysis is unnecessary for this article, which intervenes in discussions on gene-editing technologies to reveal a multifaceted EU-level imaginary, and underscore its importance in the framing of instruments of legal regulation at that level of governance. We do not seek to trace the overlaps, (dis)similarities, and (dis)continuities between the imaginary relating

23 The internal market is defined by Article 26(2) TFEU as 'an area without internal frontiers in which the free movement of goods, persons, services and capital is ensured'. The establishment of the internal market is required by Article 3(3) Treaty on European Union (TEU). The internal market also extends to the European Economic Area, which comprises EU Member States and Norway, Liechtenstein, and Iceland.

24 Under Article 6(a) TFEU. Article 168 essentially permits limited action in order to tackle serious cross-border threats to health. Although Article 168(5) TFEU provides that the EU legislature may 'adopt incentive measures' that are designed to, *inter alia*, 'protect and improve human health and in particular to combat the major cross-border health scourges', this specifically excludes 'any harmonization of the laws and regulations of the Member States'. In addition, Article 168(7) TFEU provides the responsibility of the Member States for the 'definition of their health policy and for the organization and delivery of health services and medical care' is respected. Legislation under Article 114 TFEU and Article 168 TFEU is adopted using the ordinary legislative procedure set out in Article 294 TFEU.

25 Regulation (EC) 1907/2006 Concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, Amending Directive 1999/45/EC and Repealing Regulation (EEC) 793/93 and Regulation (EC) 1488/94 as well as Directive 76/769/EEC and Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC, OJ 2006 L 136/3; Directive 2006/121/EC amending Directive 67/548/EEC on the Approximation of Laws, Regulations and Administrative Provisions Relating to the Classification, Packaging and Labelling of Dangerous Substances in Order to Adapt it to Regulation (EC) 1907/2006 Concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) and Establishing a European Chemicals Agency, OJ 2006 L 136/281.

26 See Article 2(5)(a) Regulation (EC) 1907/2006, *Id.*, which states that the REACH legislation does not apply to the extent that a substance is used in medicinal products and Article 2(6), which states that it does not apply to medical devices, covered by the *leges speciales* discussed in this article.

27 For example, anti-monopoly laws can determine the feasibility of research into new health technologies, see: Biotechnologies and International Human Rights, *supra* note 10; Marcus Pilgerstorfer, *EU Law and Policy on Pharmaceuticals Marketing and Post Market Control including Product Liability*, in Research Handbook on EU Health law and Policy 156 (Tamara K. Hervey et al. eds., 2017); Johan W. van de Gronden and Catalin S. Rusu, *EU Competition Law and Policy and Health Systems*, in Research Handbook on EU Health Law and Policy 267 (Tamara K. Hervey et al. eds., 2017); Aurélie Mahalatchimy, *Regulating Medicines in the European Union*, in Oxford Handbook of Comparative Health Law (Tamara K. Hervey and David Orentlicher eds., 2020).

28 See note 6 above.

to human gene-editing technologies and that applicable to other new and emerging technologies.[29] These kinds of analyses would require far more space than can be provided in this article-length piece.

Nevertheless, this article also sheds light on how the multifaceted imaginary found in the framing of various instruments of legal regulation at the EU level does not develop *de novo* but instead may reflect approaches taken at the national level.[30] In particular, national approaches to legal regulation of gene editing attempt to avoid repeating past ideas about eugenics and human enhancement, which led to the horrors of Nazism. As we shall explain, this is certainly found in the key facet of safeguarding morality and ethics, in particular, and places a limit on EU-level regulation in respect of gene editing.[31] We do not consider alternative imagined futures, which may be apparent in, for instance, consultations, proposals, and drafts of new legislation before the EU's legislature,[32] except where they are relevant to our argument.

Our central finding is that the facets of an EU-level imaginary are found within the framing of individual instruments of EU legal regulation and that as a whole, the imaginary has both regulatory effects and amounts to an attempt to legitimate that regulation. As part of the frame of this regulation, the multifaceted imaginary serves to legitimate regulation that steers behaviour toward the development of human somatic gene-editing technologies. Through this, the imaginary helps to realize the EU's market-oriented goals, ie relating to its internal market and economy. In addition, we suggest that the imaginary found in EU-level regulation may serve to contrast the EU, and its imagined future and identity, with that taking shape elsewhere, such as in China. We make our argument by examining each of the key facets of the imaginary in turn, before concluding with our broader thoughts.

II. FIRST KEY FACET: TENSION AROUND NATURALNESS

We begin by considering the tension around naturalness as it is built into the framing of EU-level regulation of gene-editing technologies. This is especially apparent in relation to legislation on patents and GMOs.

29 This could of course form the basis for rich and fruitful further investigation.

30 For discussion, see: R. Alta Charo, *The Legal and Regulatory Context for Human Gene Editing|Issues in Science and Technology* (2016) (accessed Jan. 10, 2020); Judit Sándor, *The Ethical and Legal Analysis of Embryo Preimplantation Testing Policies in Europe*, in Screening the Single Euploid Embryo 353 (E. Scott Sills ed., 2015); Julian Savulescu, *Genetic Interventions and the Ethics of Enhancement of Human Beings*, in The Oxford Handbook of Bioethics 516 (Bonnie Steinbock ed., 2007); The Wellborn science: Eugenics in Germany, France, Brazil, and Russia (Mark B. Adams ed., 1990).

31 For example, in Germany, Article 5 Embryo Protection Act 1990 makes it a punishable offence for a person to 'artificially alter the genetic information of a human germline cell', or who 'uses a human germline cell with artificially altered genetic information for the purpose of fertilization'. In France, its Criminal Code makes eugenic and reproductive cloning crimes against humanity. Furthermore, Article 16–4 French Civil Code (1804, amended 2017) specifically excludes 'modification of genetic traits with the purpose of modifying the germ line'.

32 In the context of the law examined, which is adopted on the basis of Article 114 TFEU, the relevant procedure for its adoption is Article 294 TFEU, ie the ordinary legislative procedure. This provides the 'EU legislature' comprises the European Commission (proposal), the European Parliament and Council (joint adoption).

II. A. Patents

Patents are a tool for commercializing an invention and facilitating its translation from the laboratory bench to clinical prescription and application. The EU's Legal Protection of Biotechnological Inventions Directive[33] (Biotechnology Directive) aims to steer behaviour and stimulate innovation that recognizes the risks of developing new technologies and seeks to minimize them. It does so through the incentive of exclusive rights to benefit from the innovation through patent protection.[34] Patents provide a temporary and territorial monopoly for which the holder can prohibit or authorize the invention's exploitation. It is noteworthy that patenting does not authorize the patent holder to implement that invention but only entitles their exclusive exploitation. Regardless of whether or not a product is patented, market approval is required for medical inventions entering the EU market.[35] In what follows, we discuss the criteria for patentability under the Biotechnology Directive and relate them to the tension around naturalness.

The ability to demonstrate innovation, and distinguish from what occurs in nature, or naturalness, is crucial to the criteria for patentability.[36] These provide that the innovation must be new or novel, involve an inventive step, and be 'susceptible of industrial application'.[37] Under these criteria, the isolation or production by means of a technical process of the sequence or partial sequence of a gene, for instance, may be a patentable invention, even if the structure of that element is identical to that of a natural element. Here, the work on a natural element is highlighted for the purpose of patent. In other words, human intervention by means of 'a technical process' transforms a discovery into an invention. The limits on what inventions can possibly be patented are of central importance, particularly to gene-editing technologies.

A key recital begins by stating 'patent law must be applied so as to respect the fundamental principles safeguarding the dignity and integrity of the person'. We shall return to this point later on, where we consider it in relation to safeguarding morality and ethics as the second key facet of the imaginary underpinning the framing of EU law in this area. What is of importance here is the overlap of this moral and ethical facet with the tension around naturalness itself as a limit to patentability. This is made apparent in the next part of the recital:

> '*the human body*, at any stage in its formation or development, including germ cells, and the simple discovery of one of its elements or one of its products, including the sequence or partial sequence of a human gene, *cannot be patented*.'

33 Directive 98/44/EC on the Legal Protection of Biotechnological Inventions, OJ 1998 L 213/13.

34 Amanda Odell-West, *Exclusions in Patent Law as an Indirect Form of Regulation of New Health Technologies in Europe*, in European Law and New Health Technologies (Mark L. Flear et al. eds., 2017). See also: Tamara K. Hervey and Hari Black, *The European Union and the Governance of Stem Cell Research*, 12 Maastricht J. Eur. Comp. Law 3 (2005).

35 Recital 14 Directive 98/44/EC, *supra* note 33. The European Medicines Agency (EMA) deals with the evaluation and supervision of medicinal products authorized at the European level in the EU.

36 For discussion, see: Rochelle C. Dreyfuss, Jane Nielsen and Dianne Nicol, *Patenting Nature—A Comparative Perspective*, 5 J. Law Biosci. 550 (2018).

37 Article 3 Directive 98/44/EC, *supra* note 33.

The recital concludes by stating 'these principles are in line with the criteria of patentability proper to patent law, whereby *a mere discovery cannot be patented*'.[38] Here, we can see that patentability relies upon a certain degree of human intervention that serves to distinguish an invention from a discovery.

Building on the above statement, another recital states:

> 'Whereas, therefore, it should be made clear that *an invention based on an element isolated from the human body or otherwise produced by means of a technical process, which is susceptible of industrial application, is not excluded from patentability*, even where the structure of that element is *identical to that of a natural element*, given that the rights conferred by the patent *do not extend to the human body and its elements in their natural environment*.'[39]

This indicates that an invention can be based on the act of 'isolating' an element from the human body. This further underscores the significance of the tension around naturalness as a key facet of the imaginary found within the framing of this legislation. 'Invention' is distinguished from—and indeed leverages—that which is naturally occurring. But rights in relation to the invention do not extend to its source in nature: the human body and its elements.

This distinction between naturalness and invention thus provides the basis for the former as the first key facet of the imaginary embedded in the framing of EU-level legal regulation. The key facet, as part of framing, makes it possible to construct the legislation, including its rationale and detailed provisions. The recitals that frame the EU's legislation state 'in the field of genetic engineering, research and development require a considerable amount of high-risk investment and *therefore only adequate legal protection can make them profitable*'.[40] The pre-emption of diverse national patent protection regimes and the establishment of a single EU-level regime for biotechnological inventions is aimed at reducing the risks to investments made by developers.

Since Article 114 TFEU is the legal basis of this legislation, it is ultimately justified by the idea that differences in the legal protection of biotechnological inventions between countries within the internal market would create barriers to trade.[41] This rationale was challenged in *Netherlands v Parliament and Council (Biotechnology)*.[42] However, the Court of Justice of the EU (CJEU) found that the Biotechnology Directive 'in fact aims to prevent damage to the unity of the internal market which might result from the Member States' deciding unilaterally to grant or refuse such protection'.[43] This rationale was affirmed elsewhere in the Biotechnology Directive:

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38 Recital 16, *Id.* Also see Article 5(1) *Id.* (emphasis added).

39 Recital 20, *Id.* Also see Article 5(2) *Id.* (emphasis added). In addition, Recital 21 *Id.* states '*Whereas such an element isolated from the human body or otherwise produced is not excluded from patentability since it is, for example, the result of technical processes* used to identify, purify and classify it and to reproduce it outside the human body, techniques which human beings alone are capable of putting into practice and which nature is incapable of accomplishing by itself' (emphasis added). For discussion, see: Alice Yuen-Ting Wong and Aurélie Mahalatchimy, *Human Stem Cells Patents—Emerging Issues and Challenges in Europe, United States, China, and Japan*, 21 J. World Intellect. Prop. 326–355 (2018).

40 Recital 2 Directive 98/44/EC, *supra* note 33 (emphasis added).

41 Recitals 5, 6 and 7, *Id.*

42 Case C-377/98 Netherlands v. Parliament and Council [2001] ECR I-7079 (ECLI:EU:C:2001:523).

43 *Id.*, para. 18.

> 'uncoordinated development of national laws on the legal protection of *biotechnological inventions* in the [EU] could lead to further disincentives to trade, to the *detriment of the industrial development of such inventions* and of the smooth operation of the internal market.'[44]

The market-oriented rationale for the Biotechnology Directive focuses on a harmonized approach to protecting biotechnological inventions within the internal market. As a key facet of the imagined future to be brought into being through this legislation, the tension around naturalness operates to provide the understanding of inventions that are eligible for protection for commercial exploitation, and legitimate this instrument of legal regulation.

II. B. Genetically Modified Organisms

The tension around naturalness, as a key facet of the imaginary within the framing of EU legal regulation, is also apparent in the GMO Directive. Our focus here is on the tension around naturalness as it provides the very foundation for the understanding of GMOs and the scope of the GMO Directive. Under this Directive, GMOs are defined such that it '*means an organism, with the exception of human beings*, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination'.[45] The GMO Directive applies to the 'deliberate release into the environment' or 'placing on the market . . . as or in products' of GMOs.[46] The GMO Directive is usually applicable to food, but it is also relevant to ATMPs that use GMOs, ie gene editing, which are developed and marketed within the EU.

ATMPs that are, or consist of, GMOs, would be covered by both the ATMP legislation (which is considered in the next section) and the GMO legislation. Indeed, the GMO Directive remains relevant in that it contains requirements in relation to clinical trials and an equivalent environment risk assessment for ATMPs that are, or consist of, GMOs.[47] These requirements are in addition to those required for other ATMPs. ATMPs that are, or consist of, GMOs as defined in the GMO Directive, are being developed. Moreover, among ATMPs authorized thus far, gene therapy medicinal products usually contain GMOs. For instance, Zolgensma, a recent gene therapy medicinal product that has obtained a marketing authorization valid throughout the EU from May 18, 2020, is a genetically modified vector[48] infused into a vein to treat spinal muscular atrophy for patients with inherited mutations affecting specific genes.[49]

Within the GMO Directive, and by contrast with the approach under the Biotechnology Directive, naturalness is juxtaposed against artificialness rather than invention.

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44 Recital 7 Directive 98/44/EC, *supra* note 33 (emphasis added).

45 Article 2(2) Directive 2001/18/EC on the Deliberate Release into the Environment of Genetically Modified Organisms and Repealing Directive 90/220/EEC, OJ 2001 L 106/1 (emphasis added). There is another piece of legislation, see: Directive 2009/41/EC on the Contained Use of Genetically Modified Micro-Organisms, OJ 2009 L 125/75.

46 Article 1, Directive 2001/18/EC, *Id.*

47 Article 5, *Id.* Also see EMA, *Guideline on Environmental Risk Assessments for Medical Products Consisting of, or Containing, Genetically Modified Organisms (GMOs)*, EMEA/CHMP/BWP/473191/2006—Corr.

48 A vector is an administration system for gene transfer that can be viral or non-viral. Zolgensma is a genetically modified adenoviral vector.

49 Spinal muscular atrophy is a serious condition of the nerves that causes muscle wasting and weakness. EMA, *Zolgensma, European Public Assessment Report* (2020), EMA/200482/2020.

The very definition of GMO, noted above, refers to the alteration of genetic material 'in a way that *does not occur naturally* by mating and/or natural recombination'.[50] Here, that which is artificial is understood in relation to what it is 'not', ie it does not occur naturally. Naturalness is given a precise meaning as occurring through mating and/or natural recombination. Put differently, the tension around naturalness is that which gives meaning to and makes possible an understanding of artificialness.

This operation of the tension around naturalness has also been recently seen in the CJEU's jurisprudence on the GMO Directive. In *Confédération paysanne and Others v Premier ministre and Ministre de l'Agriculture, de l'Agroalimentaire et de la Forêt*, the CJEU considered whether products based on the gene-editing technique mutagenesis fall within the GMO Directive. The CJEU held that organisms obtained by mutagenesis, including through gene editing such as CRISPR techniques, are to be classified as GMOs, as long as the techniques and methods of mutagenesis alter the genetic material of an organism in a way that does not occur naturally.[51]

Although this jurisprudence has been adopted for GMOs in plants, it can be foreseen that the same reasoning should also be applicable, at least in principle, for methods of mutagenesis in human genetic material.[52] In addition, the judgment also makes clear how the distinction between what is natural or not—ie the tension around naturalness as a facet of the imaginary found in the framing of the GMO Directive—is ultimately a legal construction, and one that also operates as a tool of legitimation. Indeed, the tension around naturalness, specifically, where naturalness is juxtaposed against and gives rise to an understanding of artificialness, underpins and legitimates the very classification of GMO.

Legally distinct from a GMO, an organism is defined as 'any biological entity capable of replication or of transferring genetic material'[53] and falls outside the scope of the GMO Directive. However, the CJEU found that it follows organisms obtained by means of techniques/methods of mutagenesis must be considered as 'altered in a way that does not occur naturally by mating and/or natural recombination', as per the definition of GMOs noted above.

To support its reasoning, the CJEU applied its usual teleological and purposive method of interpretation to reflect on the 'general scheme'[54] of the GMO Directive as one of the factors used in its interpretation. The general scheme also juxtaposes naturalness with artificialness, organisms with GMOs. Indeed, as the CJEU found, Annex 1 A, Part 1, of the GMO Directive provides that genetic modification 'occurs *at least* through the use of the techniques listed there'. More particularly, while Part 1 'does not explicitly refer to techniques/methods of mutagenesis, that fact is *not such as to exclude organisms obtained by means of those techniques/methods from coming under the definition of a GMO . . .*'.[55] The inclusion of *inter alia* in the first sentence of Part 1

50 Emphasis added.

51 Case C-528/16 Confédération paysanne and Others v. Premier ministre and Ministre de l'Agriculture, de l'Agroalimentaire et de la Forêt [2018] (ECLI:EU:C:2018:583).

52 This should be confirmed in the forthcoming study of the European Commission regarding the status of novel genomic techniques under Union law in light of the Court of Justice's judgment in Case C-528/16, *Id*., as requested by the Council of the EU.

53 Article 2(1) Directive 2001/18/EC, *supra* note 45.

54 C-528/16 Confédération paysanne and Others, *supra* note 51, at para 31 (emphasis added).

55 *Id*. at para. 34 (emphasis added).

was taken in its literal and accurate meaning to provide 'the list of genetic modification techniques in that part is *not exhaustive*', and as such 'that list *cannot be regarded as excluding genetic modification techniques other than those to which it specifically refers*'.[56]

The upshot, therefore, is that organisms obtained by means of techniques/methods of mutagenesis fall within the definition of GMO under this legislation. The GMO Directive does not, however, apply to organisms obtained through certain mutagenesis techniques. That is, those techniques/methods that have conventionally been used in several applications and have accumulated a long safety record.[57] According to the CJEU, the latter does not exclude from the scope of the GMO Directive, 'organisms *obtained by means of new techniques/methods of mutagenesis* which have appeared or have been mostly developed *since Directive 2001/18 was adopted*'.[58] Another interpretation 'would fail to have regard to the intention of the EU legislature'.[59] Here, it appears that the naturalness of organisms is maintained thanks to conventional use and a long safety record, notwithstanding any potential hint of artificialness arising through the techniques/methods through which they are obtained. The track record of safety, accumulated through several applications, seems central to the maintenance of naturalness for these organisms, at least in terms of their formal legal classification. By being demonstrably safe, these organisms appear analogous to others and distinguishable from GMOs, which require oversight to ensure their safe development.

The tension around naturalness not only provides a basis for the specific legal provisions in the GMO Directive, but it also links to the rationale for the legislation and its legitimation. The rationale is again market-oriented, since the GMO Directive is based on Article 114 TFEU. Specifically, it is:

> 'necessary to approximate the laws of the [Member States] . . . concerning the deliberate release into the environment of GMOs and to ensure the safe development of industrial products utilising GMOs.'[60]

The divide between naturalness and artificialness makes possible—or perhaps is the consequence of—an assumption that the harms or hazards that may arise from GMOs can be controlled.[61] Put differently, what is artificial (GMOs) and natural (certain organisms, even despite their genetic modification and according to the methods used)

56 *Id.* at para 35 (emphasis added).

57 C-528/16 Confédération paysanne and Others, *supra* note 51, at para. 37. In reaching this view, the CJEU refers to specifc parts of Directive 2001/18/EC, *supra* note 45, ie Recital 17, which provides as much and is used by the CJEU to interpret Article 3(1), relating to exemptions, that the GMO Directive does not apply to organisms obtained through the techniques of genetic modification listed in Annex I B to that directive, including these certain kinds of mutagenesis. Thus, the Member States remain free (under their laws) to subject such organisms to the obligations laid down by the GMO Directive or to other obligations, consistent with the free movement of goods, especially under Articles 34–36 TFEU [prohibition on restrictions on free movement (Articles 34 and 35) subject to derogations on the grounds of *inter alia* public morality, public policy or public security; the protection of health and life of humans, animals or plants (Article 36)]. See: Aurelie Mahalatchimy, *Genome Editing and the European Union*, in Genome Editing and the Law Around the World (Judit Sandor ed., 2019).

58 *Id.* at para 51 (emphasis added).

59 *Id.*

60 Recital 7 Directive 2001/18/EC, *supra* note 45.

61 For discussion, see: Maria Lee, EU Regulation of GMOs: Law and Decision Making for a New Technology (2008).

is distinguished within the law. What is artificial is deemed susceptible to control so as to ensure safety. What is natural is implicitly deemed safe and thus control through legal regulation is not necessary. In summary, the CJEU's decision further refines and embeds the tension around naturalness within the framing of the GMO Directive. This tension becomes a key tool of legitimation and part of the larger imaginary of EU legal regulation of gene-editing technologies.

The framing of both the Biotechnology Directive and GMO Directive reflects the tension around naturalness. Within the former, the tension around naturalness provides the basis upon which inventions are constructed and understood as eligible for protection through patents. Within the latter, the tension around naturalness operates in a similar way by providing the ground upon which artificialness is constructed and understood as the basis for legislation (on GMOs). In summary, the tension around naturalness is foundational and facilitative of both the Biotechnology Directive and the GMO Directive. The tension around naturalness found in the framing of these pieces of legislation is the first part of the multifaceted imaginary on gene-editing technologies found at the EU level of legal regulation.

III. SECOND KEY FACET: SAFEGUARDING MORALITY AND ETHICS

The second key facet of the imaginary, safeguarding morality and ethics, is apparent in what is regarded as moral or ethical to be patented; what research can be funded by the EU research framework programmes; and the products that can be commercialized as gene-editing technologies in Europe. These considerations are found in EU legislation on patents, research funding, and clinical trials for ATMPs.

III. A. Patents

The Biotechnology Directive also reflects another key facet of the imaginary built into the framing of EU-level regulation of gene-editing technologies: safeguarding morality and ethics. The latter is apparent in several recitals that frame the Biotechnology Directive and become further concretized in Article 6.[62] This specific provision provides that inventions are to be 'considered unpatentable where their *commercial exploitation* would be contrary to *ordre public* or morality'.[63] To assist in the interpretation of this provision, there is a non-exhaustive and indicative list of processes to which the exclusion from patentability applies. We discuss this list, since it is through it that safeguarding morality and ethics operates and becomes further embedded within the framing and content of the Biotechnology Directive.

The first three items on the list relate directly to humans bodies and their elements. Certain types of intervention in human bodies and their elements are considered immoral and unethical. The second of these relates most directly to gene-editing technologies, since it mentions 'processes for *modifying the germ line genetic identity of human beings*'.[64] The first item is also relevant in that it relates to the human genome by

62 Recitals 36–40 Directive 98/44/EC, *supra* note 33.

63 Article 6, *Id.* (emphasis added). The morality clause in Article 53(a) European Patent Convention has been revised so that it corresponds to the Directive, see Rules 23b–23e of the Implementing Regulations. For critical comment on this change, see Deryck Beyleveld and Roger Brownsword, Human Dignity in Bioethics and Biolaw 197, 199 (2002).

64 Article 6(2)(b) Directive 98/44/EC, *supra* note 33, reflecting Recital 40 (emphasis added).

excluding from patentability 'processes for cloning *human beings*'.[65] The third item relates to the human genome, albeit more indirectly, in that it excludes from patentability inventions that involve 'uses of *human embryos* for industrial or commercial purposes'. Notably, this exclusion does not apply to inventions for therapeutic or diagnostic purposes.[66] The final item on the list is also relevant to gene-editing technologies for humans; in that, it relates to a risk/benefit test, stating that 'processes for *modifying the genetic identity of animals* which are *likely to cause them suffering without any substantial medical benefit* to man or animal, and also animals resulting from such processes'.[67]

In these ways, safeguarding morality and ethics, a key facet of the imagined future found at the EU-level of governance, appears in the framing and specific provisions of the Biotechnology Directive. This key facet operates to exclude from patentability gene-editing technologies that modify or relate to the human germ line in particular. Although the list of processes to which the exclusion from patentability applies is non-exhaustive,[68] it also implies that, subject to the medical treatment exception to patentability, which we discuss in the next section, certain processes for human gene editing may be patentable.[69] Indeed, commercial exploitation of inventions 'could be' moral and ethical, and thus 'patentable', provided that they 'do not' modify the human germ line, result in its cloning in human beings or use through human embryos.

CJEU jurisprudence on the indicative list of processes to which the exclusion from patentability under Article 6 Biotechnology Directive applies, further embeds and stabilizes the safeguarding of morality and ethics within the framing of the legislation and, in turn, as a key facet of the wider imaginary of the future found at the EU level. In *Oliver Brüstle v Greenpeace*, the CJEU clarified the meaning of 'human embryo' in Article 6. The CJEU observed, consistent with its earlier decision in *Netherlands v Parliament and Council (Biotechnology)*, that while the 'the text of the Directive does not define human embryo', the term:

> 'must be regarded, for the purposes of application of the Directive, as designating *an autonomous concept of European Union law which must be interpreted in a uniform manner throughout the territory of the Union*.'[70]

Having determined that there must be an EU-specific meaning of 'human embryo', but wary that 'the definition of human embryo is a very sensitive social issue in many Member States, marked by their multiple traditions and value systems',[71] the CJEU built on the indicative list. It did so by underlining its role in the reference procedure from the national court for interpretation of EU law, ie in this case, Article 6 Biotechnology Directive.[72] The reference meant that the CJEU could not 'broach

65 Article 6(2)(a) *Id.*, reflecting Recital 40 (emphasis added).
66 Article 6(2)(c) *Id.*, reflecting Recital 42 (emphasis added).
67 Article 6(2)(d) *Id.*, reflecting Recital 45 (emphasis added).
68 Recital 38, *Id.*
69 As such in principle, the criterion of an invention being 'susceptible of industrial application', under Article 3(1) *Id.* could apply even where there is no commercial application.
70 Case C-34/10 Oliver Brüstle v. Greenpeace [2011] ECR I-9821 (ECLI:EU:C:2011:669), at para. 26 (emphasis added).
71 *Id.* at para 30.
72 The preliminary reference procedure, in particular Article 267(b) TFEU.

questions of a medical *or ethical nature*', and as such it 'must restrict itself to a *legal interpretation* of the relevant provisions of the [Biotechnology] Directive'.[73]

The absence of a definition of 'human embryo' in the Biotechnology Directive or wider EU law meant that the CJEU had to construct one through its usual teleological and purposive approach to interpretation, which was mentioned above. In this case, reference to and application of this approach led the CJEU to refer to the rationale for the Biotechnology Directive provided in the recitals:[74]

> 'the preamble to the Directive states that although it seeks to promote investment in the field of biotechnology, use of biological material originating from humans *must be consistent with regard for fundamental rights and, in particular, the dignity of the person*. *Recital 16* in the preamble to the Directive, *in particular, emphasizes that "patent law must be applied so as to respect the fundamental principles safeguarding the dignity and integrity of the person"*.'[75]

Fleeting references elsewhere in the Biotechnology Directive[76] do not include any to the provisions on human dignity and integrity of the person in the EU's Charter of Fundamental Rights (EU Charter).[77] At the time of the Biotechnology Directive's introduction, the latter had not been drafted, and it was only given equal status to the TFEU and Treaty on European Union (TEU) in 2009.[78] However, since 2009, provisions of EU law must be interpreted by the CJEU, and applied by the other institutions and Member States when implementing EU law, in light of the EU Charter as a primary source of law.[79] Absent references to the EU Charter, it appears the CJEU thought references within Biotechnology Directive itself were sufficient to ensure that it could perform its duty to interpret Article 6.[80]

The CJEU made references to the recitals *inter alia* the statement that 'processes, the use of which offend against human dignity . . . are obviously also excluded from patentability'.[81] In light of these references, the CJEU found that Biotechnology

73 Case C-34/10 Oliver Brüstle, *supra* note 70, at para. 30 (emphasis added). In this regard the CJEU referred to Case C-506/06 Sabine Mayr v. Bäckerei und Konditorei Gerhard Flöckner OHG [2008] ECR I-1017.

74 The CJEU referenced its approach to interpretation by stating it the meaning of the term 'must be determined by considering, *inter alia*, the context in which they occur and the purposes of the rules of which they form part'—Case C-34/10 Oliver Brüstle, *supra* note 70, at para. 31.

75 Case C-34/10 Oliver Brüstle, *supra* note 70, at para. 32 (emphasis added).

76 Instead, there is reference to fundamental rights as provided for in the European Convention on Human Rights and the general principles of EU law (drawn from national constitutional traditions) (Directive, at para. 43), and ethical principles as advised by the European Commission's advisory European Group on Ethics in Science and New Technologies (Directive 98/44/EC, *supra* note 33, at para. 44).

77 Articles 1 and 3, respectively, Charter of Fundamental Rights of the European Union (EU Charter), OJ 2012 C 326/391. Both provisions are informed by Case C-377/98 Netherlands v. European Parliament and Council, *supra* note 42. Article 3 is also informed by Convention on Human Rights and Biomedicine, adopted by the Council of Europe (ETS 164 and additional protocol ETS 168) (also known as the Oviedo Convention). Only a handful of EU Member States are not State Parties to the Oviedo Convention—including Belgium, Germany, Ireland, and the former Member State (as of 31 Jan. 2020) of the United Kingdom. See: Explanations Relating to the Charter of Fundamental Rights, OJ 2007 C 303/17.

78 The EU Charter was given equal status to the Treaties under Article 6 TEU, under the Treaty of Lisbon, which came into force on Dec. 1, 2009.

79 Article 51 EU Charter, *supra* note 77.

80 The CJEU's role is set out in Article 19 TEU.

81 Recital 38 Directive 98/44/EC, *supra* note 33.

Directive's 'context and aim . . . show that the EU legislature intended to *exclude any possibility of patentability [of human embryos] where respect for human dignity could thereby be affected*'.[82] Consequently, the CJEU ruled that it 'follows that the concept of "human embryo" within the meaning of . . . [the indicative list in the Directive] must be understood in a wide sense'.[83]

Of course, the creation of a definition of 'human embryo' in EU internal market law, through the Biotechnology Directive, and one that the CJEU revised in *International Stem Cell Corporation v Comptroller General of Patents*,[84] is an important consequence of the legislation.[85] But the CJEU's insistence that there had to be such a definition, and the rationale for it gives insight into the operation of the safeguarding of morality and ethics as a key facet of the imaginary underpinning EU legal regulation of gene-editing technologies. In particular, development of the 'human embryo' exception to the Biotechnology Directive centralizes human dignity, as found in the recitals framing the legislation, as an integral component of the safeguarding of morality and ethics. It has been argued elsewhere that the CJEU has taken 'at least impliedly, a moral stance'.[86] Moreover, as such the CJEU has been criticized for 'refusing to say it refers to ethics while it does'.[87] While we accept these points, our analysis makes clear how the legal interpretation adopted by the CJEU allows it to use human dignity—ie safeguarding morality and ethics as part of a wider imaginary—as a legitimating support for EU involvement and a restrictive approach in all patenting relating to the human embryo, which of course includes gene-editing techniques applied to the human embryo.

In this way, the CJEU's jurisprudence both refines and further embeds and constructs the safeguarding of morality and ethics within the framing of the Biotechnology Directive and, in turn, as a key facet of the EU-level imaginary relating to gene-editing

82 Case C-34/10 Oliver Brüstle, *supra* note 70, at para. 34 (emphasis added).

83 *Id.*, para. 34. At para. 36, the CJEU held that the classification 'human embryo' applies to, eg 'a non-fertilized human ovum into which the cell nucleus from a mature human cell has been transplanted and a non-fertilized human ovum whose division and further development have been stimulated by parthenogenesis'. The criterion for determining whether these fall within the term 'human embryo' is that they are 'capable of commencing the process of development of a human being just as an embryo created by fertilization of an ovum can do so'.

84 See Case C-364/13 International Stem Cell Corporation v. Comptroller General of Patents [2014] (ECLI:EU:C:2014:2451), where the CJEU followed the opinion of its Advocate General in order to qualify the criterion in para. 36 of Case C-34/10 Oliver Brüstle, *supra* note 70, further. The CJEU held that the criterion must be understood as meaning a non-fertilized human ovum must have the 'inherent capacity to develop into a human being' (at para. 28). As such 'where a non-fertilized human ovum does not fulfil that condition, the mere fact that that organism commences a process of development is not sufficient for it to be regarded as a "human embryo"' (at para. 29). Thus, where 'an unfertilised human ovum whose division and further development have been stimulated by parthenogenesis did have the capacity to develop into a human being' it is to be classified as a 'human embryo' and cannot be patented (as in Case C-34/10 Oliver Brüstle, *supra* note 70, at para. 31). But where 'according to current scientific knowledge, a human parthenote, due to the effect of the technique used to obtain it, is not as such capable of commencing the process of development which leads to a human being', it is not to be classified as a 'human embryo' and can be patented (as in Case C-364/13 International Stem Cell Corporation, at para. 33 and para. 37).

85 Case C-364/13 International Stem Cell Corporation, *Id.*, para. 27, citing Recitals 3 and 5–7 Directive 98/44/EC, *supra* note 33.

86 Enrico Bonadio, *Stem Cells Industry and Beyond: What is the Aftermath of Brüstle?*, 3 Eur. J. Risk Regul. 93 (2012).

87 Brice de Malherbe and Jean- Christophe Galloux, *L'Arrêt Brüstle: de la Régulation du Marché à l'Expression des Valeurs*, 9 Propriete Industrielle 7 (2012), at 11.

technologies. As such the facet of safeguarding morality and ethics further legitimates and justifies the Biotechnology Directive, and its rationale of fostering the internal market and competitiveness of the EU's domestic biotechnology industry. Safeguarding morality and ethics helps to steer the EU's patenting field toward certain types of inventions such as that using adult cells.[88] Trade secrets over manufacturing processes thus become increasingly critical in light of the limitations on patentability.[89] The EU's intellectual property law provides that any invention using gene-editing techniques could, therefore, be legitimately exploited and marketed within the internal market as an ATMP. We develop this point further below.

III. B. Research Funding and Clinical Trials

Safeguarding morality and ethics, as a key facet of the EU-level imaginary built into the framing of legal regulation of gene-editing technologies, is also clearly apparent in the EU's framework for funding research and legislation on clinical trials. Both of these essentially relate to research processes and are therefore considered together.

Regarding the funding of research, the EU adopts multi-annual Framework Programmes (FPs) to support research and technological development. These FPs contain an obligation to comply with the ethical requirements, with ethical review of all research projects to be funded, as well as specific prohibitions that have been clarified over time.[90] The current Regulation establishing Horizon 2020—the latest FP for research and innovation (2014–2020)[91]—requires compliance with 'ethical principles and relevant national, Union and international legislation, including the Charter of Fundamental Rights of the European Union and the European Convention on Human Rights and its Supplementary Protocols'.[92] This legislation also excludes from EU funding:

> '(a) research activity aiming at human cloning for reproductive purposes; (b) research activity intended to modify the genetic heritage of human beings which could make such changes heritable (21); (c) research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer.'[93]

In addition to these limitations, the EU does not fund research prohibited in all Member States or in particular Member States. For instance, research on embryonic stem cells can be funded in some countries where they are allowed, and not in the ones where

88 Alison Abbott, *Stem Cells: The Cell Division*, 480 Nature 7377 (2000).

89 Stephen Jenei, *EU's Court of Justice: Stem Cells Unpatentable If An Embryo Is Destroyed*, Patent Baristas (2011), http://www.patentbaristas.com/archives/2011/10/24/eus-court-of-justice-stem-cells-unpatentable-if-an-embryo-is-destroyed/(accessed Aug. 5, 2020).

90 For a more detailed presentation of EU legislation on funding for new health technologies, see: Estelle Brosset and Aurelie Mahalatchimy, *EU Law and Policy on New Health Technologies*, in Research Handbook in EU Health Law and Policy 197 (Tamara K. Hervey et al. eds., 2017).

91 Regulation (EU) 1291/2013 Establishing Horizon 2020—the Framework Programme for Research and Innovation (2014–2020) and Repealing Decision 1982/2006/EC, OJ 2013 L347/104.

92 Article 19(1), *Id.*

93 Article 19(3), *Id.*

they are forbidden, as long as the exclusion of funding in (c) above does 'not prevent [EU] funding of subsequent steps involving human embryonic stem cells'.[94]

With these clear limitations, the current FP reflects the safeguarding of morality and ethics. This facet of the imagined future of gene-editing technologies to be brought into being by EU-level legal regulation limits the scope of EU funding of research into them, and through these limitations legitimates EU involvement. Indeed, there are double restrictions on research on human germline editing: the exclusion regarding the heritability of gene modification; and the exclusion regarding the creation of human embryos solely for the purpose of research or for the purpose of stem cell procurement.

As for clinical trials, they are subject to specific regulation, with the Clinical Trials Directive[95] dating from 2001 being replaced by the new Clinical Trials Regulation.[96] The latter entered into force on June 16, 2014, but is unlikely to come into operation before 2021, until an audit demonstrates the various technical systems described below can function.[97] In what follows, we refer to the Clinical Trials Regulation, as the relevant parts for our discussion continue the approach under the Clinical Trials Directive. We focus on the scope, purpose, and rationale for the Clinical Trials Regulation, and subsequently the protections it provides for trial participants. We explain how each of these relates to safeguarding morality and ethics and through it legitimating regulation in relation to gene-editing technologies.

The Clinical Trials Regulation maintains the provision in the Clinical Trials Directive that '*no* gene therapy trials may be carried out which *result in modifications to the subject's germ line genetic identity*'.[98] The ATMP Regulation reflects this through its own specific provision.[99] Within these clear limits, relating directly to safeguarding morality and ethics, ie that somatic gene therapy trials are permitted, the Clinical Trials Regulation provides for the planning, performance, reporting, and archiving of quality, safety, and efficacy data on gene-editing technologies for their marketing and commercialization as ATMPs.[100]

The purpose and rationale of the Clinical Trials Regulation relate to the key facet of safeguarding morality and ethics. Indeed, the very definition of clinical trials in the

94 Point 12 of the European Commission, *Statement on Article 19* Regulation *(EU) 1291/2013*, *Id.;* European Commission, *Annex to the Legislative Resolution: Statements by the Commission [on the Horizon 2020—Framework Programme for research and innovation]* (2013), www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P7-TA-2013-0499+0+DOC+XML+V0//EN (accessed Sep. 24, 2020). For the principle, see Article 19(4) Regulation (EU) 1291/2013, *supra* note 91.

95 Directive 2001/20/EC on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use, OJ 2001 L 121/34. This requires the European Commission to establish principles relating to GCP and detailed rules in line with those principle.

96 Regulation (EU) 536/2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC, OJ 2014 L 158/1.

97 Under Article 99, *Id.*, the legislation shall not apply earlier than 28 May 2016. Directive 2001/20/EC, *supra* note 95 continues to apply in a transitional period, see Article 98, *Id.* See further: https://ec.europa.eu/health/human-use/clinical-trials/regulation_en (accessed Sep. 24, 2020).

98 Recital 75, Article 90 Regulation (EU) 536/2014, *Id* (emphasis added).

99 Article 4 Regulation (EC) 1394/2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) 726/2004, OJ 2007 L 324/121, citing Article 9(6) Directive 2001/20/EC, *supra* note 95 which is now found in Article 90 Regulation (EU) 536/2014, *supra* note 96.

100 As noted in Recital 16 Regulation (EC) 1394/2007, *Id.*

Clinical Trials Regulation highlights their alignment to the requirements for marketing and the overriding focus of that on product safety for humans. This focus amounts to an instantiation of the key facet of safeguarding morality and ethics. Under the Clinical Trials Regulation, clinical trials are clarified as being a type of clinical study[101] (which includes for ATMPs[102]), ie an investigation of medicinal products in humans that essentially attempts to ascertain 'the safety and/or efficacy of those medicinal products'.[103]

A large part of the rationale for the adoption of the Clinical Trials Regulation also reflects the key facet of safeguarding morality and ethics. Experience under the Clinical Trials Directive gave rise to concerns that differences in its application in the EU's (now) 27 Member States[104] would undermine scientific research.[105] Factors that may undermine scientific research, including multi-center trials in different Member States,[106] make it harder to meet moral and ethical obligations relating to the pursuit and refinement of knowledge for medical benefit.

In order to make the latter possible, and meet the moral and ethical obligations intrinsic to scientific research, it became necessary to revise the applicable law through the adoption of the Clinical Trials Regulation. The latter introduces an EU portal[107] that serves as a single entry point for the submission of an application for the authorization of clinical trials within Member States,[108] and an EU database for the storage

101 Article 2(2)(1) Regulation (EU) 536/2014, *supra* note 96 provides 'clinical study' 'means any investigation in relation to humans intended: (a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; (b) to identify any adverse reactions to one or more medicinal products; or (c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal products'.

102 Article 2(1)(a) Regulation (EC) 1394/2007, *supra* note 99 defines ATMPs as any of the following medicinal products for human use: a gene therapy medicinal product as defined in Part IV Annex I Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use, OJ 2001 L 311/67; a somatic cell therapy medicinal product, as defined in Part IV Annex I Directive 2001/83/EC; a tissue engineered product, as further clarified in Article 2(1)(b) and (c) Regulation (EC) 1394/2007.

103 The definition in Article 2(2)(1) REGULATION (EU) 536/2014, *supra* note 96, cited in *supra* note 101, is very similar to that under Article 2(a) Directive 2001/20/EC, *supra* note 95, particularly the objective: a 'clinical trial' means 'any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of one or more investigational medicinal product (s), and/or to identify any adverse reactions to one or more investigational medicinal product (s) and/or to study absorption, distribution, metabolism, and excretion of one or more investigational medicinal product (s) *with the object of ascertaining its (their) safety and/or efficacy*' (emphasis added).

104 Up from 15 in 2001—and 28 prior to the UK's withdrawal from the bloc on Jan. 31, 2020. Regulation (EU) 536/2014, *supra* note 96, on clinical trials, like other internal market law also applies in the non-EU members of the European Economic Area: Norway, Liechtenstein, and Iceland. See *supra* note 23.

105 Since around the mid-1980s, the preference was to opt for the adoption of directives rather than regulations, and yet, the increase in the number of Member States and diversity in their legal cultures (including in implementation and compliance with EU law) has led to a more general growing preference for regulations.

106 Recital 4 Regulation (EU) 536/2014, *supra* note 96.

107 Arts 5, 16, and 80, *Id.*

108 In the first instance, the trial sponsor shall propose the reporting Member State. In the event that this proposal is declined, more detailed rules determine which Member State shall report: see Article 5, *Id.*

of the application and related data.[109] The EU portal also provides the means for communication of, *inter alia*, the result of the application.[110]

To introduce these changes, make it easier to generate safety data, and in turn, fulfil moral and ethical obligations relating to scientific research, it was also necessary to reconsider the form of the legislative instrument on clinical trials.[111] As summarized in the Clinical Trials Regulation, the adoption of a regulation 'would present advantages for sponsors and investigators, for example in the context of clinical trials taking place in more than one Member State, *since they will be able to rely on its provisions directly [before national courts]*'.[112] In contrast, the Clinical Trials Directive (as a directive) could only be relied upon directly in very specific circumstances.[113] This meant that in most cases, domestic implementing legislation was applicable.[114]

The adoption of an EU regulation (the Clinical Trials Regulation) more uniformly harmonizes and enhances the efficacy and uniformity of EU law. This in turn makes it easier to meet moral and ethical obligations relating to the pursuit and refinement of knowledge for medical benefit. In these various ways, a large part of the rationale for the adoption of the Clinical Trials Regulation also reflects and embeds the key facet of safeguarding morality and ethics. This is both as a general concern for scientific research, but also as it forms part of the EU-level imaginary framing legal regulation of gene-editing technologies.

The key facet of safeguarding morality and ethics is also apparent in the dual legal basis for the adoption of the Clinical Trials Regulation: Article 114 TFEU and Article 168(4)(c) TFEU, which provide objectives that are 'pursued simultaneously' and 'one is not secondary to another'.[115] This joint legal basis provides that the Clinical Trials Regulation is aimed at ensuring the good functioning of the internal market and the establishment of high standards of quality and safety for medicinal products,

109 Article 81, *Id.*

110 Article 8, *Id.*

111 Consistent with the legal basis for internal market legislation under Article 114 TFEU.

112 Recital 5 Regulation (EU) 536/2014, *supra* note 96 (emphasis added). Article 288 TFEU defines directives and regulations. A directive is 'binding, as to the result to be achieved, upon each Member State to which it is addressed, but shall leave to the national authorities the choice of form and methods'. In contrast, a regulation has 'general application. It shall be binding in its entirety and directly applicable in all Member States'.

113 Under the doctrine of direct effect. The CJEU has found that provided they are sufficiently clear, precise, and unconditional the provisions of directives can be relied upon before Member State courts as against the Member State only (that is, not individuals), but only where their deadline for implementation has passed and the Member State has not properly implemented them (Case C-71/74 Van Duyn v. Home Office [1974] ECR 1337 (ECLI:EU:C:1974:133); Case C-148/78 Pubblico Ministero v. Tullio Ratti [1979] ECR 1629 (ECLI:EU:C:1979:110)). By contrast the CJEU has found that regulations are capable of being relied upon before Member State courts as against the Member State and individuals, as appropriate, from the date they enter into force and become applicable (as specified in the specific instrument) (Case C-39/72 Commission v. Italy [1973] ECR 101 (ECLI:EU:C:1973:13)).

114 In the case of the UK, for example, the Clinical Trials Directive was adopted into domestic law by its transposition through the Medicines for Human Use (Clinical Trials) Regulations 2004, Statutory Instrument No. 1031/2004.

115 Recital 82 Regulation (EU) 536/2014, *supra* note 96. Article 168(4)(c) provides the base for 'measures setting *high standards of quality and safety* for medicinal products and devices for medical use'. Article 168(4)(c) is a derogation to Article 6(a), as per Article 2(5) TFEU which provides for EU action to support, coordinate or supplement the Member States, and is in accordance with Article 4(2)(k), which provides for shared competence in 'respect of *common safety concerns* in public health matters' (emphasis added).

respectively.[116] Safeguarding morality and ethics, a key facet of the imagined future to be brought into being by the Clinical Trials Regulation, is reflected in the focus in this legal foundation on ensuring product safety within the internal market.[117] It is on this basis that safeguarding morality and ethics provides a 'bioethical stamp' that ensures that products can be legitimately marketed within the internal market.

The Clinical Trials Regulation also makes extensive reference to the 'protection of trial subjects'.[118] A key recital to the Clinical Trials Regulation references the Clinical Trials Directive's 'extensive set of rules for the protection of subjects' and states '[t]hese rules should be upheld'.[119] The key facet of safeguarding morality and ethics is reflected in these protections and its foundation—noted in the recital as stemming from '[h]uman dignity and the right to the integrity of the person' as recognized in the EU Charter.[120]

Specific protections include risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by research ethics committees and Member States' competent authorities, and rules on the protection of personal data.[121] These protections underscore that in respect of gene-editing technologies, as it is more generally, safeguarding morality and ethics is usually seen as a field to be dealt with at the national level.[122]

A principle way in which safeguarding morality and ethics are assured comes through the stress on informed consent. The key recital on informed consent states how the '[EU] Charter requires that any intervention in the field of biology and medicine cannot be performed without free and informed consent of the person concerned'.[123] There are references to informed consent throughout the Clinical Trials Regulation,[124] including additional protections for those who are incapable of giving legal consent to participate in clinical trials (which includes children).[125]

The rules on good clinical practice (GCP) found in further legislation[126] (which will be replaced in line with the application of the Clinical Trials Regulation[127]) provides another area where the safeguarding of morality and ethics is further inflected. This legislation is supplemented by detailed guidance established by the EMA (the EU counterpart to the US Food and Drugs Administration), in accordance with the International Conference on Harmonisation of Technical Requirements for Registration

116 Recital 82, *Id.*
117 Recital 8, *Id.*
118 Chapter V, *Id.*
119 Recital 27, *Id.*
120 *Id.*
121 Recital 67, *Id.*
122 Mariachiara Tallacchini, *Governing by Values. EU Ethics: Soft Tool, Hard Effects*, 47 Minerva 281 (2009).
123 Recital 27 Regulation (EU) 536/2014, *supra* note 96.
124 For instance: Recitals 15, 17, 44, 76, and 80, Article 3, and Ch. V (on protection of subjects and informed consent), *Id.*
125 Especially Article 31 and Article 32, *Id.*
126 Directive 2005/28/EC Laying Down Principles and Detailed Guidelines for Good Clinical Practice as Regards Investigational Medicinal Products for Human Use, as well as the Requirements for Authorization of the Manufacturing or Importation of Such Products, OJ 2005 L 91/13.
127 For the state of play at time of publication, see European Commission, *Implementation measures by the Commission in the Context of* Regulation *(EU) No 536/2014—Overview and State of Play*, http://ec.europa.eu/health/files/clinicaltrials/overview_clinical_trials.pdf (accessed Sep. 24, 2020).

of Pharmaceuticals for Human Use (usually referred to as simply 'ICH').[128] GCP, in addition to good laboratory practice relating to early stages clinical trials carried out in laboraties, focuses on the rights of individual trial subjects ensuring the 'rights, safety, *dignity and well-being of subjects are protected and prevail over all other interests*'.[129]

The EU database mentioned above collates information on the content, commencement, and termination of clinical trials. This information is subject to protections for confidentiality and invokes the right to privacy—which again reflects the safeguarding of morality and ethics. Cross-references to EU data protection legislation[130] are also embedded throughout EU law on clinical trials. The protection of individual privacy essentially serves to legitimate the focus on regulating for product safety.

Overall, therefore, the Clinical Trials Regulation embeds and reflects the safeguarding of morality and ethics as a key facet of the framing of EU-level legal regulation of gene-editing technologies. This is apparent in the framing of the Clinical Trials Regulation itself and its legal bases; in the specific provisions on protections; related legislation and guidance; and systems for implementation. The safeguarding of morality and ethics through these legitimates the Clinical Trials Regulation, in particular as it applies to gene-editing technologies.

Read together, the Biotechnology Directive, the current FP for research funding, and the Clinical Trials Regulation suggest how there has been sufficient consensus across the EU's Member States to build the safeguarding of morality and ethics as a key facet of the imagined future to be brought into being through EU-level legal regulation. The issue of morality and ethics generally, as well as in relation to gene-editing technologies, is usually seen as a field to be dealt with at the national level.[131] For example, the European Commission considers that 'regulating on ethical matters is the competence of Member States'.[132]

Nevertheless, at least in respect of the examples discussed here, the backdrop of broadly shared historical experiences of eugenics and human enhancement among EU Member States,[133] and the need to ensure the functioning of the internal market, has helped to justify harmonization—although limited—of morality and ethics. This underlines how imagined futures 'are also built from imaginaries of the past'.[134] The EU's legislature has chosen to ensure that the safeguarding of morality and ethics is made part of the EU-level collective imaginary and, in turn, reflected in the framing of EU law. In doing so, it is possible to limit the potential for a repeat of the past. In reflecting concerns about the past, the facet of safeguarding morality and ethics helps to justify and legitimate the harmonization of morality and ethics at the EU level of governance.[135]

128 EMA, *E6: Guideline for Good Clinical Practice*, CPMP/ICH/135/95.

129 Article 3(a), Regulation (EU) 536/2014, *supra* note 96 (emphasis added).

130 Currently: Regulation (EU) 2016/679 on the Protection of Natural Persons with Regard to the Processing of Personal Data and on the Free Movement of Such Data, and Repealing Directive 95/46/EC (General Data Protection Regulation), OJ 2016 L 119/1.

131 Tallacchini, *supra* note 122.

132 European Commission, *Report on Embryonic Stem Cell Research Provides Basis for Discussion on Ethics* (2003), IP/03/506.

133 See *supra* note 31.

134 Beckert, *supra* note 19, at 91.

135 Tallacchini, *supra* note 122.

IV. THIRD KEY FACET: PURSUING MEDICAL OBJECTIVES FOR THE PROTECTION OF HUMAN HEALTH

The third and final key facet of the imaginary built into the framing of EU-level legal regulation for gene-editing technologies regards the pursuit of medical objectives for the protection of human health. This key facet is apparent in EU legislation relating to patents and the marketing of ATMPs.

IV. A. Patents

The recitals framing the Biotechnology Directive also provide a separate medical treatment exception that methods of therapeutic, diagnostic, and surgical treatment on the human or animal body are not patentable in the EU's internal market.[136] This also applies to such methods involving gene-editing. For humanitarian reasons, these methods are not to be deemed inventions capable of patent protection. Physicans and healthcare workers should not be prevented from providing suitable medical treatment to patients. The medical and public health benefit of these methods overrides arguments for their status as potential patentable inventions.[137] However, a distinction is made between medical methods and medical products. This exception does not cover medical products with therapeutic, diagnostic, or surgical purposes. As such it is possible to obtain patents for 'products' used in therapeutic, diagnostic, and surgical 'methods'. Put differently, it is the methods themselves, rather than products used in such methods, that are excluded from patentability.[138] The pursuit of medical objectives for the protection of human health, manifest in this exclusion on patentability, is a key facet of the imaginary built into the framing and provisions of the Biotechnology Directive.

The exclusion from patentability of therapeutic, diagnostic, and surgical treatment methods practised on the human body means that their developers are not able to exclusively benefit from their commercialization, and that they can be used widely by third parites without the need for a licence of exploitation. Despite excluding methods of therapeutic, diagnostic, and surgical treatment from patentability, the Biotechnology Directive still provides scope to obtain patent protection for gene-editing technologies. That is, provided they are 'not' medical methods practised on the human body (*in vivo*) and 'not' contrary to its other provisions on 'ordre public' and morality (as discussed above). There is, in short, the potential for patentability of gene-editing technologies (including limited *in vitro* methods), but not the 'methods' that use and deploy them directly on the human body (*in vivo*). The distinction between medical products and medical methods potentially steers the commercial trajectory of gene-editing technologies toward the former. The pursuit of medical objectives for the protection of human

136 Recital 35 Directive 98/44/EC, *supra* note 33 mirroring Article 53(c) European Patent Convention 2000. The former states the 'Directive *shall be without prejudice to the provisions of national patent law* whereby processes for *treatment* of the human or animal body by surgery or *therapy and diagnostic methods* practised on the human or animal body are *excluded from patentability*'. For discussion, see: Wong and Mahalatchimy, *supra* note 39.

137 As mentioned earlier, medical benefits also constitute an exception to the limitations on the patentability of inventions using human embyos for therapeutic or diagnostic purposes.

138 Recital 35 Directive 98/44/EC, *supra* note 33; Article 53(c) European Convention on the Grant of European Patents (European Patent Convention). See also: Phoebe H. Li, *3D Bioprinting Technologies: Patents, Innovation and Access*, 6 Law Innov. Technol. 282 (2014).

health, as a facet of the imaginary built into the framing of the Biotechnology Directive, underpins this distinction and in turn legitimates the legislation.

The value of gene-editing patents can also be limited by other legal provisions, including those relating to marketing. Indeed, the Biotechnology Directive is clear that a 'patent for invention *does not authorize the holder to implement that invention*, but merely entitles him to prohibit third parties from exploiting it for industrial and commercial purposes'.[139] The Directive builds on this, in relation to marketing, to state:

> '. . . consequently, *substantive patent law cannot serve to replace or render superfluous national, European or international law which may impose restrictions or prohibitions* or which concerns the monitoring of research and of the use or commercialisation of its results, *notably from the point of view of the requirements of public health, safety, environmental protection, animal welfare, the preservation of genetic diversity and compliance with certain ethical standards*.'[140]

For the purposes of this provision, 'European law' can be understood to encompass EU law. As we turn next to explain, EU law also regulates the marketing of gene-editing technologies. The Biotechnology Directive does not replace the following or make it superfluous.

IV. B. Advanced Therapy Medicinal Products

Gene-editing technologies are likely to fall under the EU's ATMP Regulation.[141] This piece of legislation provides gene-editing technologies with the regulatory pathway toward marketing across the EU's Member States, which comprise the territory of the internal market. Patent holders have exclusive rights to the marketing of their products—and they can grant licences to others to market products that make use of patented inventions. In terms of the products, which may or may nor be subject to a patent, the scope of the ATMP Regulation is particularly important. For that reason, in what follows, we focus our attention on the scope, benefits, and practical limits of this pathway to marketing gene-editing technologies under the ATMP Regulation.

The ATMP Regulation covers gene therapy medicinal products, somatic cell therapy medicinal products, tissue engineered products, and combined ATMPs (bringing together one of the first three categories with a medical device).[142] These catagories of medicinal products must be 'either prepared industrially or manufactured by a method involving an industrial process' and 'intended to be placed on the market in Member States'.[143]

Among the legal category of ATMPs, medicinal products based on gene-editing technologies may be classified as gene therapy medicinal products[144] although this

139 Recital 14 Directive 98/44/EC, *supra* note 33 (emphasis added).

140 *Id.* (emphasis added).

141 Regulation (EC) 1394/2007, *supra* note 99.

142 Article 2, *Id.*

143 Article 2 Directive 2001/83/EC, *supra* note 102.

144 Article 2.1 Part IV of Annex I Directive 2001/83/EC, *Id.*, provides gene therapy medicinal products as 'a biological medicinal product which has the following charcateristics: (a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; (b) its therapeutic,

pathway may not be easy to navigate.[145] The ATMP Regulation focuses on gene therapies containing or consisting of recombinant nucleic acid. Consequently, Mourby and Morrison suggest that nucleic acids not produced by recombination, and protein-based molecules which are also gene-editing techniques, may fall outside the scope of the definition of gene therapy medicinal products within the ATMP Regulation.[146] Nevertheless, it appears the Committee for Advanced Therapies, which provides scientific recommendations on the legal classification of ATMPs, have already made a wide application of the definition of gene therapy medicinal products beyond the clear presence of recombinant nucleic acid.[147]

Where genetically modified cells are being developed for manufacturing purposes in the development of medicinal products, and do not use the target genetic sequence for therapeutic use, the resulting products based on gene-editing techniques will be classified as cell therapy medicinal products or tissue engineered products. Where genetically modified cells do use the target genetic sequence for therapeutic use, the medicinal products based on gene-editing techniques will be classified as gene therapy medicinal products.[148] Finally, where a product falls within the definitions of both somatic cell therapy medicinal products and gene therapy medicinal products, or tissue engineered products and gene therapy medicinal products, it shall be considered as a gene therapy medicinal product.[149]

In case of any doubt as to the potential applicability of the EU's Medical Devices Regulations[150] to a gene-editing technology that has a medical device component, the ATMP Regulation provides:

> 'whatever the role of the medical device, the pharmacological, immunological or metabolic action of these cells or tissues should be considered to be the principal mode of action of the combination product. Such combination products should always be regulated under this Regulation.'[151]

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prophylactic or diagnostic effect relates directly to the recombinant nucleic acide sequence it contains, or to the product of genetic expression of this sequence'.

145 Martina C. Cornel et al., *Moving Towards a Cure in Genetics: What is Needed to Bring Somatic Gene Therapy to the Clinic?*, 27 Eur. J. Hum. Genet. 484 (2019).

146 Miranda Mourby and Michael Morrison, *Gene Therapy Regulation: Could In-Body Editing Fall Through the Net?*, 28 Eur. J. Hum. Genet. 979 (2020).

147 *Id.*

148 EMA, *Draft Guideline on Quality, Non-Clinical and Clinical Aspects of Medicinal Products Containing Genetically Modified Cells* (2018), EMA/CAT/GTWP/671639/2008 Rev. 1.

149 Article 2(5) Regulation (EC) 1394/2007, *supra* note 99.

150 Within the EU, the applicable law is subject to transition from a trio of directives to a duo of regulations, which are due to apply fully from May 26, 2021: Regulation (EU) 2017/745 on Medical Devices, Amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and Repealing Directives 90/385/EEC and 93/42/EEC, OJ 2017 L117/1; Regulation (EU) 2017/746 on In Vitro Diagnostic Medical Devices and Repealing Directive 98/79/EC and Decision 2010/227/EU, OJ 2017 L117/176. Implementation of this legislation is left to national competent authorities, including, at the time of writing, the UK's Medicines and Healthcare Products Regulatory Agency. The competent authorities designate notified bodies to assess medical device conformity with 'essential requirements'. The focus in conformity assessments is on the intended purpose and risk of a device. Where a conformity assessment finds a medical device to be compliant with the regulations, the manufacturer of the device can brand it with the CE (Conformité Européenne) mark and trade it within the EU internal market.

151 Recital 4 Regulation (EC) 1394/2007, *supra* note 99.

The centralized procedure involving the EMA is applicable to gene-editing technologies (falling within the scope of the ATMP Regulation). This procedure is compulsory for products derived from biotechnology (which obviously includes gene-editing ATMPs).[152] Products that represent a significant scientific, therapeutic, or technical innovation or that benefit public health can also make use of this route to marketing. The centralized procedure gives access to the entire market of the EU and means that procedures available for other kinds of medicinal products, which require multiple applications for their marketing in several EU Member States, can be avoided.[153] Beyond the centralized procedure, the ATMP Regulation provides other legal incentives to foster the marketing of these products. These include harmonized scientific guidelines;[154] and a reduction in the fees payable to the EMA for the provision of scienctific data, amounting to a 90 per cent reduction for small and medium sized enterprises and a 65 per cent reduction for other applicants.[155]

Consistent with the safeguard clauses under Article 114 TFEU, which permit temporary measures deviating from EU legislation adopted under it by Member States,[156] the ATMP legislation includes a safeguard clause for public health grounds.[157] Public policy and public morality grounds are also available to prohibit ATMPs, but they can be used only exceptionally.[158] More specifically, the ATMP Regulation provides:

> 'The regulation of advanced therapy medicinal products at Community level *should not interfere with decisions made by Member States on whether to allow the use of any specific type of human cells*, such as embryonic stem cells, or animal cells. *It should also not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products containing, consisting of or derived from these cells*.'[159]

In relation to public morality, part of the key facet of the imaginary found in the framing of EU-level legal regulation (ie safeguarding morality and ethics), there is jurisprudence on the specific Article 36 TFEU public morality derogation to the free movement of goods under Article 34 TFEU. According to this jurisprudence, it remains 'for each Member State to determine in accordance with its own scale of values and in the form

152 Regulation (EC) 726/2004 Laying Down Community Procedures for the Authorization and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency, OJ 2004 L 136/1.

153 These procedures are the decentralized procedure, the mutual recognition procedure and the national procedures. See: Flear, *supra* note 17; Mahalatchimy, *supra* note 27.

154 For instance for each kind of ATMP, GCP, good manufacturing practices, good pharmacovigilance practices.

155 Article 16 Regulation (EC) 1394/2007, *supra* note 99.

156 See Flear, *supra* note 17.

157 Article 20(4) Regulation (EC) 726/2004, *supra* note 152 on the centralized procedure states: 'Where urgent action is *essential to protect human health or the environment*, a Member State may, on its own initiative or at the European Commission's request, suspend the use in its territory of a medicinal product for human use which has been authorized in accordance with this Regulation' (emphasis added).

158 Recital 7 Regulation (EC) 1394/2007, *supra* note 99 states as regards 'any specific type of human cells' the ATMP Regulation 'should also not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products containing, consisting of or derived from these cells'. Recital 13 states: '*Member States should be able exceptionally to prohibit* the use in their territory of medicinal products for human use *which infringe objectively defined concepts of public policy and public morality*' (emphasis added).

159 Recital 7 Regulation (EC) 1394/2007, *supra* note 99 (emphasis added).

selected by it the requirements of *public morality* in its territory'.[160] Consistency in the treatment of domestically and imported goods is essential for the successful use of this derogation.[161] The latter is therefore available to prohibit ATMPs that make use of, for example, embryonic stem cells. The narrow scope of these grounds for temporary national measures ensures a focus on product safety for marketing. Moral and ethical concerns, for instance, can provide scope to exclude certain gene-editing ATMPs from a national market, but there is limited scope for using these.

More broadly, the ATMP Regulation does not explicitly prohibit the marketing of germline gene-editing technologies—or simply their use. There was an attempt by the European Parliament to include a provision in the ATMP Regulation that there could be no marketing authorization granted to ATMPs modifying the human germ line. However, these amendments were rejected by the Council of Ministers.[162]

Still, in order to be marketed as ATMPs, gene-editing technologies, like any other ATMP or indeed medicinal product,[163] require clinical trials data that demonstrate their quality, safety, and efficacy. There can be no marketing of ATMPs without clinical trials data. As discussed above, the Clinical Trials Regulation provides a clear prohibition on gene therapy clinical trials resulting in modifications to the subject's germ line genetic identity. The latter prohibition would seem to preclude the marketing of ATMPs that modify the human germ line when linked to relevant EU law.

This interpretation gains added credibility given the ATMP Regulation states:

> 'This Regulation respects the fundamental rights and observes the principles reflected in the Charter of Fundamental Rights of the European Union and also takes into account the Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine.'[164]

As we noted above, the EU Charter also provides that the ATMP Regulation, as EU law, must also be interpreted consistently with it, and this includes its provisions on human dignity and integrity of the person.[165] The latter provision, Article 3, provides that in the field of medicine and biology, 'the prohibition of eugenic practices, in particular those aiming at the selection of persons, the prohibition on making the human body and its parts as such a source of financial gain, and the prohibition of the reproductive cloning of human beings' must be respected.

In short, when read in light of the Clinical Trials Regulation and the EU Charter, it seems that it is not possible to use the ATMP Regulation to market ATMPs that modify the human germ line. The provisions in these instruments, when read together, appear

160 Case C-34/79 Regina v. Maurice Donald Henn and John Frederick Ernest Darby [1979] ECR 3795 (ECLI:EU:C:1979:295), at para. 15 (emphasis added).

161 Case C-121/85 Conegate Limited v. HM Customs & Excise [1986] ECR 1007 (ECLI:EU:C:1986:114).

162 European Commision, *Draft Report on the Proposal for a* Regulation *of the European Parliament and of the Council on Advanced Therapy Medicinal Products and Amending DIRECTIVE 2001/83/EC, and* Regulation *(EC) 726/2004* (2006) (COM(2005)0567—COD2005/0227).

163 As Recital 6 Regulation (EC) 1394/2007, *supra* note 99 states the ATMP is a '*lex specialis*, which introduces additional provisions to those laid down' in DIRECTIVE 2001/83/EC, *supra* note 102.

164 Recital 8 Regulation (EC) 1394/2007, *supra* note 99.

165 See *supra* note 77.

to effectively prohibit ATMPs that involve the modification of the human germ line, despite the lack of explicit exclusion in the ATMP Regulation itself. As such, the pursuit of medical objectives for the protection of health, as framed within EU law, legitimates the development of human somatic gene-editing technologies by opposition to human germline gene-editing technologies.

Yet, the scope of the ATMP Regulation is limited to specific kinds of medicinal products, as the definition of its scope makes clear. As such, the ATMP Regulation does not prohibit the marketing of products that are not manufactured at the industrial scale or 'other than' medicinal products. Indeed, this would depend on the specific instruments and provisions of EU law and/or national laws applicable to the products in question. Nor does the ATMP Regulation, as recognized in its recitals, 'interfere with decisions made by Member States on whether to *allow the use* of any specific type of human cells, such as embryonic stem cells, or animal cells'.[166]

This provision encompasses the *use* of one type of cells that are specifically not capable of being patented under the Biotechnology Directive (embryonic stem cells). The provision also seems to permit the use of both somatic and germ line cells, irrespective of whether they have been edited. Nevertheless, the classification of cell therapy medicinal products in the ATMP Regulation as somatic cell therapy medicinal product explicitly shows the intent to exclude medicinal products based on embryonic or germ line cells therapy from the cell therapy medicinal products legal category among ATMP, as long as neither embryonic cells nor germ line cells are somatic cells. Given the specific prohibition in the Clinical Trials Regulation, 'use' here appears to be for purposes 'other than' clinical trials for medicinal products, including ATMPs. 'Use' could, therefore, encompass other kinds of clinical and preclinical research for purposes other than the marketing of medicinal products, ie falling outside the scope of the Clinical Trials Regulation (noted above).

As with the other examples of EU legislation applicable to gene-editing technologies considered above, the overarching focus of the ATMP Regulation is on marketing, since it was adopted under Article 114 TFEU on the internal market. This is apparent in the rationale for ensuring that ATMPs are subject to the centralized procedure:

> 'This procedure should also be compulsory for advanced therapy medicinal products in order to overcome the scarcity of expertise in the Community, ensure a high level of scientific evaluation of these medicinal products in the Community, preserve the confidence of patients and medical professions in the evaluation and *facilitate Community market access for these innovative technologies*.'[167]

The Biotechnology Directive and ATMP Regulation set-up specific frames regarding gene-editing-based technologies used for the pursuit of medical objectives for the protection of human health. The former provides limited scope for patentability, specifically, by allowing patents on products rather than methods in the medical field. This in turn facilitates the wide use of gene-editing methods of therapeutic, diagnostic, and surgical treatment on the human or animal body. This can be done without the need for costly licences from patent holders, while at the same time promoting the development

166 Recital 7 Regulation (EC) 1394/2007, *supra* note 99 (emphasis added).

167 Recital 9, *Id.* (emphasis added).

of products based on gene-editing, which may be patentable. The ATMP Regulation provides various incentives for the marketing of such products, not least the centralized marketing authorization procedure.

Both the Biotechnology Directive and ATMP Regulation reflect the importance that is given to pursuing medical objectives for the protection of human health as a key facet of the imaginary built into the framing of EU-level regulation of gene-editing technologies. As a key facet of the EU-level imaginary embedded in framing, pursuing these objectives further legitimates and justifies regulation prohibiting the development of medicines modifying the human germ line genetic identity.

V. CONCLUSION

In this article, we illuminated the three key facets of the imaginary found in the framing of instruments of legal regulation in respect of human gene-editing technologies at the EU level of governance. These facets are the tension around naturalness; safeguarding morality and ethics; and the pursuit of medical objectives for the protection of human health. These facets are distributed between various legal instruments, which when looked at together, make it possible to view a multifaceted imaginary or imagined future across them.

Our analysis makes clear that this imaginary conjures into being a future in which technoscience within the EU is steered toward particular innovations, ie which exploit human somatic gene editing for new medicinal products, but avoid editing of the human germ line itself for new medicinal products. This analysis suggests how the EU's legislature behaves in the way Jasanoff explains: 'it often falls to legislators, courts, the media, or other institutions of power to *elevate some imagined futures above others, according them a dominant position for policy purposes*'.[168] We have not sought to reveal the various possible alternative futures that may be reflected in, for example, consultations and proposals for new legislation on gene-editing technologies, or different iterations of legislation through the legislative process.

Nevertheless, our analysis has shown that the three facets appear together in only one of the legal instruments applicable to human gene-editing technologies, ie the Biotechnology Directive. One explanation for this may be that the Biotechnology Directive is the oldest instrument among the legislation applicable to gene-editing technologies. The long process of adoption for this text established for the first time key limitations for the patentability of biotechnologies. The latter comprise the key facets of the EU-level imaginary built into the framing of the Biotechnology Directive. The inclusion of such key limitations and facets may have been more necessary at the time of the adoption of the Biotechnology Directive in 1998, in order to legitimate internal market legislation, and given the absence of a specific legal base for public health before 1999.[169] The EU-level imaginary found in the framing of the Biotechnology Directive has been gradually strengthened in the subsequent legislation applicable to human gene-editing technologies.

168 Dreamscapes of modernity, *supra* note 20, at 4 (emphasis added). The focus here on 'imagined futures' tallies with Beckert, *supra* note 19 and affirms our view of a single imaginary at the EU level.

169 When ensuring a high level of human health protection 'in the definition and implementation of all Union policies and activities' was included by the Treaty of Amsterdam (entering into force in 1999) under what is now Article 168(1) TFEU and was previously Article 152 European Community Treaty.

The market-oriented focus of the legislation applicable to gene-editing technologies, and the importance of the imaginary to its legitimation, can be explained in large part by its adoption under Article 114 TFEU, the legal base for internal market legislation. This underscores the weakness of Article 168 TFEU, the EU's supporting competence in the public health field.[170] Article 114 provides far greater scope for the adoption of harmonization measures. EU law relating to clinical trials provides the sole exception among the legislation discussed, since it was adopted under Article 114 and Article 168(4)(c).

Article 168(4)(c), as a buttress for Article 114, underscores the weakness of Article 168 TFEU, and the overriding rationale and justification for the legislation adopted by the EU's legislature: product safety for marketability. The strength of Article 114, and the buttress of Article 168(4)(c), thus help to explain the market-oriented focus of legal regulation on gene-editing technologies at the EU level of governance.

What, then, does the imagined future assembled from facets found in the framing of EU-level legal regulation actually do? The analysis in this article further underscores how the concept of imaginaries, as McNeil and colleagues argue, 'seems to offer new ways to investigate the relationships among science, technology, and society'.[171] In particular, by steering, or restricting, limiting, and directing the development of human gene-editing technologies, the imaginary discussed in this article can be seen to play an important regulatory function for the internal market. This function occurs through the framing of EU legal instruments. That is, the imaginary does not play a role in itself, independent from framing; nor does it function alongside framing as an epiphenomenon.

The imaginary built into framing also plays a significant role in legitimating the market-oriented focus of legal regulation at the EU level. Specifically, through its concretization in various safeguards and limitations, and individual protections, the imaginary places a 'bioethical stamp' on the development pipeline and human gene-editing technologies eventually authorized as ATMPs for marketing purposes. This is apparent in a few key areas in various pieces of EU legislation, including what types of products and processes can benefit from a monopoly of exploitation via patents; what kinds of research activities can be funded by the EU; the definition of GMOs and how they can be safely commercialized; the performance of clinical trials; and the marketing of human gene-editing based ATMPs. Whether the legitimating function of the imaginary is successful or, relatedly, more significant than the regulatory function, is an empirical question of the kind that is outside the scope of the more normative analysis this article has aimed to provide.

Finally, the analysis also contributes to broader reflections on our starting point in this article: developments in gene editing around the world. The multifaceted imaginary found in EU-level regulation may serve to contrast the EU, and its imagined

170 Recent understandings of Article 168 TFEU suggest that it can be augmented as part of a web of competences, including Article 114 TFEU—see: Kai P. Purnhagen et al., *More Competences than You Knew? The Web of Health Competence for European Union Action in Response to the COVID-19 Outbreak*, 11 Eur. J. Risk Reg. 297 (2020).

171 Maureen C. McNeil et al., *Conceptualizing Imaginaries of Science, Technology and Society*, in The Handbook of Science and Technology Studies 435 (Ulrike Felt et al. eds., 4th ed. 2017).

future and identity,[172] with that taking shape elsewhere, currently perhaps especially in China.[173] Most notably, in restricting human germ-line editing, the imaginary of the EU, and its identity, has a particular orientation toward ethics and human rights, and their relations to markets.[174] This seems to stem from the particular negative experiences of eugenics and human enhancement in Europe. These experiences are not merely historical, but continue to be reflected in the imaginary found in the framing of EU-level of regulation and in concrete provisions, especially in the safeguards and limitations on the development of human gene-editing technologies, and individual protections for those involved in research processes.

The framings of legal regulation are not simply about what happens (or does not) here and now. They entail imagined futures, which, through their iteration in the framing of legal regulation and the shaping of specific provisions, are performed and brought into being.

172 For a similar argument on the relationship between law and identity, see Christopher Harding, *The Identity of European Law: Mapping Out the European Legal Space*, 6 Eur. Law J. 128 (2000).

173 Jon Cohen and Nirja Desai, *With its CRISPR Revolution, China Becomes a World Leader in Genome Editing*, Science (2019), https://www.sciencemag.org/news/2019/08/its-crispr-revolution-china-becomes-world-leader-genome-editing (accessed Apr. 3, 2020).

174 Relatedly, see: Flear, *supra* note 17.